

What's new in hypertension?

Since the publication of the South African Hypertension Guidelines in 2006 several landmark clinical trials have been published or presented that have far-reaching implications for the way we treat patients with hypertension. In addition, the review of a recent study that had major impact on nephrological practice has been seriously questioned.

BRIAN RAYNER, MB ChB, FCP, MMed

Division of Hypertension and Nephrology, University of Cape Town

Brian Rayner is Head of the Division of Nephrology and Hypertension at the Groote Schuur Hospital and University of Cape Town. He is a past president and executive member of the Southern African Hypertension Society. He has 55 publications in peer-reviewed journals.

COOPERATE study

The COOPERATE study reported that progression of chronic kidney disease was retarded to a greater extent with dual blockade of the renin-angiotensin system (RAS) compared with either an ACE inhibitor or angiotensin receptor blocker (ARB) alone.¹ However, in a review of the literature to prepare a meta-analysis of the effect of monotherapy or combination therapy of RAS inhibitors on proteinuria, Kunz *et al.* stated that they 'excluded 1 eligible study' because of serious implausibilities in the study that could not be resolved by the publishing journal.^{2,3} This included a highly unusual distribution of baseline variables, discrepancy in the statistical method and problems with patient satisfaction. They went on further to state: 'The number and seriousness of the inconsistencies found in the Nakoa article led us to wonder whether it is possible that this is only a case of extremely sloppy reporting or a hint to more severe problems with the data.' This trial has had a major influence on nephrological practice as many nephrologists were using combination therapy for protecting the kidney against progressive chronic kidney disease. This practice has to be reconsidered, especially in the light of the combination arm in the ONTARGET study (see below).

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ONTARGET and TRANSCEND studies

The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) compared an ACE inhibitor (ramipril 10 mg) with an ARB (telmisartan 80 mg) or with the combination of the two drugs in patients with a high

cardiovascular risk.⁴ This study was modelled on the HOPE study, and involved 25 000 patients. It showed that telmisartan was not inferior to ramipril and that telmisartan was better tolerated despite the exclusion of patients with ACE intolerance in the study. (These patients were allocated to the TRANSCEND study.) This finally settled the issue as to whether ARBs were less effective than ACE inhibitors for protecting patients against myocardial infarction. Thus the choice of ACE inhibitor or ARB for patients with high cardiovascular risk is solely determined by tolerability and cost.

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It was widely anticipated that patients in the combination arm would fare better than the ramipril group but this was not the case. The primary outcome was identical and there were significantly more problems in the combination arm with more hypotension, syncope, and renal outcomes. In a separate publication the renal outcomes were separately reported and despite a reduction of albuminuria there were significantly more patients with doubling of serum creatinine and need for dialysis in the combination arm. However, most patients required acute dialysis and given the excess number of patients with hypotension and syncope the renal events were probably related to excessive lowering of blood pressure (BP) or subclinical renovascular disease. However, this remains conjecture and it is important for clinicians to review the use of RAS combination treatment until we have further information, particularly in the light of the problems related to the COOPERATE study.

The TRANSCEND study involved patients who were intolerant to ACE inhibitors, which was defined as cough (88.2%), angioedema (1.4%), hypotension (4.1%), renal dysfunction (1%) and other reasons (8.3%).⁵ This information is important in interpreting the results, as most clinicians would not switch a patient to an ARB from an ACE inhibitor for hypotension and renal impairment. The study involved over 5 926 patients who were randomised to telmisartan or placebo and included a much higher percentage of females (43 v. 26.5%) than the ONTARGET study. There was an 8% non-significant reduction in the primary endpoint of CVS death, non-fatal MI or stroke or hospitalisation for heart failure, but for the HOPE endpoint that excluded hospitalisation for heart failure there was a significant 13% reduction in the primary endpoint ($p=0.048$). Benefits were greater for males than females. The results of TRANSCEND are very similar to the results of a large study in Australia comparing ACE inhibitors v. diuretics in hypertensive patients where there was overall 11% reduction in the primary endpoint ($p=0.05$), but the benefits were solely seen in men.⁶ The explanation of this differential effect in males and females is unknown.

In a pre-specified analysis where the results of TRANSCEND were combined with the PROFESS study (telmisartan v. placebo in patients with previous stroke) the primary endpoint became significant (7% reduction in favour of telmisartan, $p=0.026$), but a very interesting trend was noted. In the first 6 months the results for telmisartan were 12% worse ($p=0.075$), but after this period the curves diverged in favour of telmisartan (14% better, $p<0.001$). This observation again supports the contention that there was over-treatment of the blood pressure in the initial parts of the study, resulting in harm that has clouded the interpretation of ONTARGET and TRANSCEND studies.

There are important lessons to the clinicians – inhibitors of the RAS system cannot be used without due consideration to their effects on BP. It is quite clear that the notion of the lower the better for BP has to be questioned in this population. There must be a J point for BP as opposed to LDL cholesterol and given the problems of assessing BP control in patients near target due to effects of masking and white coating, my recommendation is not to target the clinic BP much below 130/80 and to make increasing use of home and ambulatory BP monitoring in high-risk

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patients to assess the degree of control in a more scientific manner. Further symptoms of hypotension are often very subtle and require careful attention to the patient's history.

HYVET study

Treatment of hypertension in the very elderly was a major unsettled issue until the publication of the HYVET study.⁷ The few data available previously on benefit v. harm were unconvincing in very elderly patients. The HYVET study recruited patients >80 years with hypertension who were otherwise healthy, and randomised them to low-dose perindopril/indapamide v. placebo. The target BP was 150/80 mmHg. The BP was 15/6 mmHg lower in the treatment arm and after 1.8 years the study was terminated because there was strong evidence of benefit in the active arm. Death from cardiovascular disease was reduced by 23%, death from any cause by 21%, stroke by 30%, and heart failure by 64%. The outcome data are very impressive and will extend the indication for hypertensive treatment to all patients of any age who are not frail and/or suffering from dementia.

The choice of a target BP of 150/80 mmHg is very interesting. Perhaps this was chosen to avoid excessive lowering of diastolic BP in attempting to achieve lower systolic targets and to prevent falls from hypotension. Interestingly, the ambulatory data presented at the recent European Society of Hypertension showed that the ambulatory BPs were substantially lower than those of the clinic. This further supports my contention that there should be more use of home and ambulatory BP monitoring in high-risk patients to avoid the effects of over-treatment.

ADVANCE study (blood pressure arm)

The ADVANCE study was a 2×2 factorial study design comparing the routine administration of a fixed combination of

perindopril and indapamide v. placebo for BP control regardless of the initial BP, and intensive v. routine glucose lowering on the risks of macrovascular and microvascular complications of type 2 diabetes at high cardiovascular (CVS) risk.⁸ The primary endpoints were composites of major macrovascular and microvascular events. In the BP arm those assigned to perindopril/indapamide had a mean reduction in systolic blood pressure of 5.6 mmHg and diastolic blood pressure of 2.2 mmHg. The relative risk of a major macrovascular or microvascular event was reduced by 9% ($p=0.04$), death from cardiovascular disease by 18% ($p=0.03$), death from any cause by 14% ($p=0.03$) and renal events by 21% (mainly worsening of microalbuminuria). Intensive glucose lowering was shown to reduce microvascular complications (mainly microalbuminuria), and the benefits of both BP and intensive glucose lowering were additive. Of interest is that in contrast to the ONTARGET study benefits in the study were seen at BPs as low as 120/80 mmHg.

ACCOMPLISH study

The results of the ACCOMPLISH study were presented in the clinical hotline session at the American College of Cardiology in March 2008 and recently published.⁹ The study compared directly fixed combination therapy of the ACE inhibitor benazepril titrated to 20 mg daily with hydrochlorothiazide titrated to 25 mg or amlodipine titrated to 10 mg for BP control in patients with systolic hypertension. Both combinations resulted in excellent BP control with little difference between the groups. However, there was a 20% reduction in fatal and non-fatal CVS events in favour of the fixed combination of ACE inhibitor and amlodipine. This study will change future guidelines with more emphasis being placed on fixed drug combinations, in particular those containing an RAS inhibitor and calcium channel blocker.

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In a nutshell

- The results of these keynote studies will have important influences on our daily practice and will almost certainly change hypertension guidelines.
- Dual therapy with ACE inhibitor and ARB is not recommended for patients at high CVS risk or for renoprotection until we have further data from controlled clinical trials.
- Over-aggressive BP control in patients meeting the entry criteria for the ONTARGET and TRANSCEND studies may be harmful, and needs to be targeted to 130/80 mmHg.
- Greater use of home and ambulatory BP monitoring needs to be instituted, especially in patients close to goal.
- Otherwise healthy >80-year-old patients with hypertension should be treated with low-dose indapamide and perindopril, and target BP should be about 150/80 mmHg.
- Patients with type 2 diabetes need to be aggressively managed for hypertension and BP target is probably 120/80 mmHg.
- Increasing use of fixed drug combinations for hypertension must be considered for improved BP control.
- An ACE inhibitor plus CCB may be preferred to ACE inhibitor plus thiazide diuretic.
- Additionally, given the results of the ADVANCE and PROGRESS studies more consideration should be given to the use of indapamide.

Single suture

Marinate your steak for a healthier meal

If you are frying steak and worried about your health, then marinate it in either beer or red wine. This is according to food scientists who measured the amounts of a family of carcinogens found in fried steak after soaking them in booze.

Cooking food increases the levels of cancer-causing compounds called heterocyclic amines (HAs). Fried and grilled meat are particularly high in these compounds because the high temperatures convert the sugars and amino acids in muscle tissue into HAs. Various substances can reduce the HA content: an olive oil, lemon juice and garlic marinade cut HAs in grilled chicken by 90% and red wine reduced HAs in fried chicken.

Now Isabel Ferreira and colleagues at the University of Porto in Portugal have looked at the effects of beer and red wine marinades on fried steak. Six hours of marinating in beer or red wine cut levels of two types of HAs by up to 90% compared with unmarinated steak.

For a third type of HA, beer was more efficient at reducing its levels than wine, cutting its levels in 4 hours, while wine took 6. Beer contains more water-retaining sugars than wine and Ferreira says that may hinder the transport of water-soluble molecules to the steak's surface, where high heat converts them into HAs.

The marinades also apparently improve the flavour and texture of the meat.

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