Twenty-four-hour blood pressure lowering: clinical need or pharmacological attribute?

Rigorous control of BP is essential for both cardiac and vascular protection. “There is a continuous relationship between blood pressure and risk of cardiovascular disease, with no lower threshold,” said Gordon T. McInnes (Department of Medicine and Therapeutics, Western Infirmary, Glasgow, United Kingdom). Small reductions in BP are associated with large risk reductions. A meta-analysis of 61 prospective observational studies covering about one million adults showed that a 2 mm Hg decrease in mean systolic BP is associated with a 7% risk reduction for mortality from ischaemic heart disease and a 10% reduction in the risk of death from stroke [1]. However, around 70% of treated hypertensive patients in Europe fail to reach recommended BP goals [2].

“It is important that we try and control blood pressure throughout the 24 hours,” Prof. McInnes said. Blood pressure follows a circadian pattern, falling at night and rising steeply on waking — the so-called morning surge. This influences cardiovascular events. Meta-analyses show that between 06:00 and 12:00 hours there is a 40% higher relative risk of acute myocardial infarction, a 29% higher risk of sudden cardiac death and a 49% higher risk of stroke, compared with the rest of the day [9]. Because antihypertensive drugs are usually taken in the morning, this is also the period when medication levels are likely to be lowest. The pharmacological profile of telmisartan gives it the longest terminal elimination half-life of the ARBs and

Blood pressure lowering: treating to prevent

A large body of evidence clearly shows that blood pressure (BP) lowering per se is a major contributor to the cardiovascular protective effects of antihypertensives. This is reflected in the recent guidelines from the European Societies of Hypertension and Cardiology (ESH/ESC), which recommend a target BP for hypertensive patients of less than 140/90 mm Hg, and treating to lower values if tolerated. “We know from epidemiology that the lower the blood pressure, the better,” said Giuseppe Mancia (University of Milan-Bicocca, Milan, Italy). Evidence also shows that high-risk patients such as those with diabetes or a history of coronary or cerebrovascular disease gain further protection from lowering BP to 130/80 mm Hg or below.

Does the evidence for the benefits of BP control per se rule out specific protective effects for particular antihypertensive drugs? This is still a matter of debate, Prof. Mancia said. However, the issue is important because reaching BP targets is difficult even under clinical trial conditions, and is rare in clinical practice. There is evidence that some drugs do have protective effects, and it is important to take these into account in strategies for cardiovascular prevention. Preventative strategies are important not only to protect high-risk individuals but to prevent others from reaching high-risk status, Prof. Mancia noted. “It is important to prevent progression from low to high risk, because once high risk is achieved it is largely irreversible,” he concluded.
therefore the longest duration of effect, Prof. McInnes noted. A study comparing telmisartan and valsartan found that telmisartan gives superior BP control over 24 hours and in the early morning surge period \(^{(9)}\). Telmisartan also had a longer duration of effect than valsartan in a missed dose study \(^{(10)}\).

### Renal protection in hypertensive patients at cardiovascular risk

Abnormal kidney function (defined as a glomerular filtration rate (GFR) of less than 60 mL per minute per 1.73 m\(^2\) of body surface area) is now recognised by European and American guidelines as a cardiovascular risk factor. People with a GFR of 45–59 have a 40% higher risk of a cardiovascular event than people with normal kidneys \(^{(9)}\). Albuminuria is a continuous variable for cardiovascular risk, George Bakris (Department of Preventive Medicine, Rush University Medical Center, Chicago, IL, USA) told delegates. Microalbuminuria indicates diffuse vascular lesions and is an important cardiovascular risk marker. It should be monitored in cardiac patients, Dr. Bakris said, and treated aggressively. “Reduction in proteinuria needs to be part of the strategy when lowering blood pressure in patients with proteinuria or kidney disease,” he stressed.

The AMADEO study compared the renoprotective effect of telmisartan with that of losartan in 860 patients with type 2 diabetes and overt proteinuria \(^{(9)}\). Patients also received antihypertensive therapy as required to ensure similar levels of BP control. The primary end points were change in albumin:creatinine and urine protein:creatinine ratios. At one year, telmisartan provided greater proteinuria reduction than losartan (p = 0.0432 and p = 0.0279, respectively). Telmisartan also gave better systolic BP control (p = 0.0558), though not statistically significant when looked at over a period of one year. The renal protective effects of telmisartan will also be studied as a secondary end point in the ONTARGET study.

### Preventing stroke in hypertensive patients at risk

In the LIFE study, theARB losartan reduced the incidence of fatal and nonfatal stroke in hypertensive patients by 25% compared with atenolol (Figure 1). BP control was similar between the two agents, but losartan was better tolerated \(^{(10)}\).

Several other studies have now shown a benefit in stroke with ARBs in comparison with other antihypertensive agents, confirmed Björn Dahlöf (Department of Internal Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden). He then discussed reasons why ARBs might be more protective against stroke than ACE inhibitors. ARBs provide a more comprehensive blockade of the negative effects of angiotensin II, while leaving the beneficial effects of the angiotensin II type 2 (AT2) receptor untouched or even enhanced. They also have fewer side effects than ACE inhibitors. There is increasing evidence that BP-independent stroke protection could be mediated by the stimulatory effect of increased angiotensin II concentrations on the AT2 receptor, he said. A meta-analysis of trial data from more than 200,000 patients showed that drugs that raise angiotensin II concentration (ARBs, calcium antagonists, and thiazides) provide better protection against stroke than those that lower them \(^{(9)}\).

Telmisartan is being evaluated in PROFESS, the world’s largest secondary stroke prevention trial. PROFESS will study over 20,000 patients with recent ischaemic stroke. It has a factorial design to test the value of telmisartan versus placebo and dipyridamole plus aspirin versus clopidogrel on time to recurrent stroke. Treatment period will be up to four years. The protective effect of a combination of telmisartan and ramipril against stroke will also be examined as part of the ONTARGET study.

### Cardiovascular protection: which individuals should be targeted?

In people without cardiovascular disease, nine risk factors predict over 90% of myocardial infarction risk, said Salim Yusuf (Division of Cardiology, McMaster University, Hamilton, ON, Canada). These are, in order of importance: blood lipids, current smoking, diabetes, hypertension, abdominal obesity, psychosocial factors, fruit and vegetable consumption, exercise level, and alcohol consumption \(^{(9)}\). Risk factors have a continuous effect, so should not be viewed as simply elevated or not elevated. In western populations, most people over the age of 50 need aggressive risk factor control, either through lifestyle changes or medication. New risk factors such as biomarkers and genetic variations currently add little to risk prediction. Markers such as social support, educational level, cognitive function, and fatigue are also important long-term predictors of outcome, even if they are not causal. Noncardiovascular comorbidities also increase risk.

### New concepts of renin–angiotensin system blockade

Thomas Unger (Charité Center for Cardiovascular Research, Berlin, Germany) discussed the concept of dual RAS blockade. Angiotensin II produces harmful effects at all
stages of the cardiovascular disease continuum. The RAS can be blocked either using ACE inhibitors or ARBs. ACE inhibitors reduce the action of angiotensin at both the AT1 and AT2 receptors. They also increase bradykinin levels, which stimulate beneficial production of nitric oxide and prostaglandins. ACE inhibitors cannot completely block the RAS, as some angiotensin is generated by other enzymes. ARBs selectively and specifically block the AT1 receptor, giving a more complete blockade of angiotensin’s proinflammatory and procoagulatory effects. Angiotensin II is still able to act on the AT2 receptor, which is thought to mediate several beneficial effects. AT2 also increases nitric oxide production, although ARBs do not stimulate the beneficial effects of kinins. ARBs are extremely well tolerated, with side effects similar to placebo in trials.

Given their different mechanisms of action, it is possible that combining ACE inhibitors and ARBs could suppress RAS more fully. This should give sustained protection from the harmful effects of angiotensin II, sustained reduction of aldosterone levels and an increase in kinins. It may also improve insulin sensitivity, especially with ARBs such as telmisartan, which selectively activate the PPAR-γ receptor. The combination could also potentially have additive effects in diabetic nephropathy and heart failure. When combined with blockade of the AT1 receptor, the angiotensin II ‘escape’ seen with ACE inhibitors stimulates the AT2 receptor.

Clinical effects of renin–angiotensin system blockade

RAS blockade has been clearly shown to provide cardiovascular protection throughout the course of cardiovascular disease, said Dr. Dahlöf. Blood pressure lowering plays a key role, but there are also benefits beyond blood pressure control. Major trials have shown that RAS blockade can also protect the kidney and blood vessels, reduce left ventricular hypertrophy, prevent diabetes, and prevent cardiovascular events and mortality, he noted. ARBs may have an advantage over ACE inhibitors in offering more complete RAS blockade and better tolerability.

Dual renin–angiotensin system blockade: existing and ongoing studies in high-risk patients

There is now a growing body of evidence to support dual RAS blockade with an ACE inhibitor and an ARB. Michael A. Weber (SUNY Downstate College of Medicine, New York, NY, USA) summarised the current state of knowledge. A metaanalysis of 10 studies showed that dual therapy gives superior blood pressure lowering compared with ACE inhibitor alone, with an average additional systolic lowering of about 5 mm Hg [13]. Compared with an ARB alone, combination therapy reduced systolic BP by about an additional 4 mm Hg. This is clear evidence for additive systolic BP lowering effects, Prof. Weber said. It is not yet clear whether the same results could be achieved using higher doses of monotherapy.

Dual blockade is being increasingly used for patients with kidney disease. In the CALM study, combination therapy gave additive benefits for both systolic BP lowering and reduction in urinary albumin:creatinine ratio in patients with hypertension, microalbuminuria and type 2 diabetes [12]. In the COOPERATE study in Japan, combination therapy slowed the progression of nondiabetic renal disease compared with monotherapy with either class [13]. Combination therapy with lisinopril and telmisartan gave a 44% mean additional reduction in urinary albumin excretion rate in patients with type 2 diabetes compared with lisinopril alone, as well as superior BP control [14]. There is good evidence that ARBs and ACE inhibitors have additive beneficial effects for renal protection and reduction of proteinuria, Prof. Weber said.

Dual RAS blockade may also be cardioprotective. In the CHARM study, 2,548 patients with heart failure or at least a 40% reduction in left ventricular ejection fraction were randomised to receive either candesartan or placebo in addition to standard background therapy, which included ACE inhibitors. The candesartan group had a significantly reduced risk of cardiovascular death or heart failure hospitalisation compared to placebo (adjusted hazard ratio = 0.85, p = 0.010) [13]. But Prof. Weber cautioned that patients with heart failure are often intolerant of aggressive RAS blocking therapy.

CHARM did not fully analyse the total or long-term cardiovascular protective benefits of combination RAS blockade, and the optimum combination and dosage have yet to be demonstrated. These questions will be addressed in the ONTARGET trial programme [14]. The design of ONTARGET and its sister study, TRANSCEND, is shown in Figure 2. Participants are high-risk patients aged over 55 years and with a broad range of cardiovascular diseases. The primary end point of ONTARGET is a composite of cardiovascular death, stroke, acute myocardial infarction, and hospitalisation for congestive heart failure. The study, which is due to report in 2008, will examine the benefits of dual RAS blockade beyond blood pressure control with this specific combination.

![Figure 2](https://example.com/figure2.png)

**THE ONTARGET TRIAL PROGRAMME**

- **ONTARGET**: n = 25,620
  - Telmisartan 80 mg + placebo
  - Ramipril 10 mg + placebo
  - Telmisartan 80 mg + ramipril 10 mg

- **TRANSCEND**: n = 5,926
  - Telsmisartan 80 mg
  - Placebo

Follow-up at six weeks and every six months

*In patients intolerant of angiotensin-converting enzyme inhibitors*

Trial acronyms

AMADEO  A prospective, randomised, double-blind, double-dummy, forced-titration, multicentre, parallel group, one year treatment trial to compare telmisartan (MICARDIS) 80 mg versus losartan (COZAAR) 100 mg, in hypertensive type 2 diabetic patients with overt nephropathy
CALM  Candesartan and lisinopril microalbuminuria
CHARM  Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
COOPERATE  Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease
LIFE  Losartan Intervention For Endpoint reduction in hypertension
ONTARGET  Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
PROFESS  Prevention Regimen For Effectively avoiding Second Strokes
TRANSCEND  Telmisartan Randomised AssessmeNt Study in ACE-i iNtolerant subjects with cardiovascular Disease

References


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