Proteinuria is associated with a reduced risk of both cardiovascular and renal events, Prof. Burgess concluded.

The results of the AMADEO (telmisartan vs. losartan in hypertensive type 2 diabetic patients with overt nephropathy) study were announced by Prof. Burgess at a well-attended scientific session. The study objective was to compare the long-term effect of telmisartan (80 mg) vs. losartan (100 mg) on proteinuria (the primary end point), and the secondary end points of other renal parameters, cardiovascular protection, and safety. Losartan is now approved for the management of diabetic nephropathy, and AMADEO is the first head-to-head comparison of its antiproteinuria effects with an other ARB.

The multicentre, double-blind, double-dummy randomised trial had a parallel group design with forced titration to the maximum recommended dose. It enrolled 860 hypertensive patients (blood pressure > 130/80 mm Hg) with type 2 diabetes and overt nephropathy, from 124 centres in 10 countries. Patients had proteinuria of ≥700 mg/g creatinine in spot urine, equivalent to 900 mg/24 hours. Serum creatinine was ≤3.0 mg/dL for women and ≤3.2 mg/dL for men. Mean age was 60 years, and 62% of the patients were male. Forty-seven per cent were Caucasian, 41% Asian and 12% black. Treatment was for one year after a four-week run-in period. In total, 419 patients were randomised to telmisartan and 441 to losartan. Other drugs, except for ARBs and ACE inhibitors, could then be added to help achieve target blood pressure, which was to go below 130/80 mm Hg. The study completion rate was 79.9%.

There is growing evidence that hypertension plays a role in the progression of chronic kidney disease and augments the adverse outcomes associated with it. Diabetic nephropathy is the leading cause of end-stage renal failure in the western world, Ellen D. Burgess (Foothills Medical Centre, Department of Medicine, University of Calgary, Calgary, AB, Canada) told delegates. Diabetic patients with renal disease typically progress from normal urinary protein levels through to microalbuminuria, when protein is detectable only on radioimmunoassay, and then to macroalbuminuria.

There is a good association between hypertension and diabetic neuropathy, Prof. Burgess said. As patients progress through proteinuria towards renal failure, the prevalence of hypertension increases. Angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE ) inhibitors have been shown to slow the progression from microalbuminuria, and may therefore be of benefit early in the disease. The IDNT and RENAAL studies showed that, in patients with overt diabetic nephropathy, the ARBs losartan and irbesartan reduced the time to doubling of serum creatinine. Losartan reduced the percentage of patients requiring renal replacement therapy (RRT) by 25%. The number needed to treat to prevent one case of RRT was 16, which is economically very significant given the huge cost of chronic renal dialysis.

Even microalbuminuria significantly increases the risk of cardiovascular events. One analysis in diabetic patients found that it increased the odds ratio to 10.02, compared with 6.52 for smoking and 2.32 for raised cholesterol. Reduction in proteinuria is associated with a reduced risk of both cardiovascular and renal events, Prof. Burgess concluded.
Blood pressure at randomisation was approximately 144/80 mm Hg in both groups. At the end of the study, blood pressure was very similar in both groups at approximately 140/77 mm Hg. "We did not get to target blood pressure, but we did as well as any other diabetic nephrology study has done," Prof. Burgess said.

Telmisartan was significantly more effective than losartan in reducing the amount of protein excreted in the urine: telmisartan reduced proteinuria by 29%, compared with 20% for losartan (p = 0.0284; Figure 1). The primary end point, change from baseline in log transformed urinary protein creatinine ratio, was 0.71 for telmisartan (95% confidence interval [CI] 0.66–0.77) and 0.80 for losartan (95% CI 0.74–0.87) [8].

![Figure 1 REDUCTION IN PROTEINURIA (UP:CR)](image)


In the secondary end points of renal function, telmisartan produced a significantly greater reduction in urine albumin:creatinine ratio compared with losartan (36% vs. 27%, p = 0.0451). However, there was no significant difference between the two treatments in mean urine sodium:creatinine ratio, estimated glomerular filtration rate, serum aldosterone or high-sensitivity C-reactive protein levels. There was also no significance in the overall composite renal or cardiovascular end points, which encompassed doubling of serum creatinine, end-stage renal disease all-cause death, and various cardiovascular end points.

AMADEO confirms the renoprotective profile of ARBs, Prof. Burgess concluded. Pharmacological differences between ARBs may have implications in renal and cardiovascular protection. Telmisartan provides superior reduction in proteinuria compared with losartan, despite similar blood pressure control. Continuous use of telmisartan may slow progression to end-stage renal disease in patients with diabetic nephropathy and reduce the risk of cardiovascular events.

Prof. Burgess commented: "The AMADEO results are encouraging for patients with type 2 diabetes because they suggest that telmisartan could improve renoprotection. It is particularly interesting that the observed effect was seen despite the study being controlled for blood pressure. This suggests that the protective benefits seen here with telmisartan are an additional attribute beyond its established blood pressure lowering effects."

**New concepts in hypertensive treatment**

A large proportion of the benefit of antihypertensive treatment is due to blood pressure lowering per se. All classes of antihypertensive drug reduce the risk of cardiovascular events, especially if blood pressure is reduced to 140/90 mm Hg or lower. Epidemiological studies and metaanalyses confirm that the lower the blood pressure, the greater the degree of cardiovascular protection. This body of evidence is behind the new European Society of Hypertension (ESH) guidelines, which state that the general population should be treated for hypertension at blood pressure of over 140/90 mm Hg, and high-risk patients should be treated at blood pressure over 130/85 mm Hg to a target of 130/80 mm Hg [6].

There is now important evidence for the need to monitor home and 24-hour mean ambulatory blood pressure as markers of cardiovascular risk, rather than relying on office blood pressure measurements, said Giuseppe Mancia (Department of Medicine, University of Milan-Bicocca, Milan, Italy). The PAMELA study, which assessed office, home, and 24-hour ambulatory blood pressure in 2,051 subjects, found that the three measured pressures provided complementary information. The results showed that mortality was lowest in individuals having all three blood pressures normal, and that it was progressively increased between patients with one, two and three types of raised blood pressure [7]. Night-time blood pressure fall, morning blood pressure surge and blood pressure variability all have prognostic significance, Prof. Mancia said. Incidence of stroke and coronary events peaks in the early morning after awakening, coinciding with the early morning surge in blood pressure. Individuals with a strong early morning blood pressure surge may have an increased risk of stroke [8].

This implies that physicians need to consider blood pressure control outside of the office. However, even controlling office blood pressure to target levels is difficult in many patients. In many of the large cardiovascular trials, mean systolic blood pressure has remained over 140 mm Hg despite the use of combination treatments. In diabetic patients, no trial has yet been able to achieve the recommended systolic blood pressure of 130 mm Hg as a mean office value. A metaanalysis of ambulatory monitoring data from 5,842 patients found that, while mean office blood pressure was lowered to 140/90 mm Hg, 24-hour ambulatory blood pressure remained well above this value [9].

Is blood pressure control the only means to protect hypertensive patients? Most have one or more other cardiovascular risk factors in addition to hypertension. Prof. Mancia and colleagues found a strong correlation between higher blood pressure and higher body mass index, higher total cholesterol, lower high-density lipoprotein–cholesterol, and higher serum glucose [10]. The primary goal of treatment is maximum reduction of total cardiovascular risk. The new ESH guidelines emphasise that this requires treatment of raised blood pressure and of all associated reversible risk factors [9].
“There is the possibility that some antihypertensive drugs have protective effects on top of the protection produced by lowering blood pressure,” Prof. Mancia continued. Possible effects include lowering risk factors such as dyslipidaemia and inflammatory markers, and preventing organ damage to the heart, kidney, and arterial endothelium. This in turn may prevent high-risk conditions like diabetes, nephropathy, metabolic syndrome, and heart failure.

A comparison of data on new-onset diabetes with different antihypertensive drugs shows that, in most trials, incidence of diabetes is less with ACE inhibitors, ARBs, and calcium channel blockers than with other drug classes [11]. The effect is strongest with drugs acting on the renin–angiotensin system (ACE inhibitors and ARBs). This is particularly important in patients who have metabolic syndrome, which puts them at high risk for diabetes. “In middle-aged individuals we do not treat to prevent an unlikely myocardial infarction but to prevent disease progression and prevent the appearance of high-risk conditions such as diabetes,” Prof. Mancia said. “Once high risk is reached, there is an element of irreversibility.”

The importance of sustained blood pressure lowering

“Small differences in blood pressure really matter,” said Gordon T. McInnes (Division of Cardiovascular and Medical Sciences, University of Glasgow, and Western Infirmary, Glasgow, UK). A metaanalysis of 61 prospective observational studies covering over 1 million patients shows that, regardless of baseline blood pressure, a 2 mm Hg reduction in mean systolic blood pressure cuts the risk of death from ischaemic heart disease by 7% and the risk of death from stroke by 10% [12].

“What we do does not seem to be enough to control blood pressure throughout the 24 hours,” Prof. McInnes noted. Only a minority of patients with controlled office blood pressure have good blood pressure control in the early morning surge period [8]. Metanalyses indicate that one in every 11 heart attacks, one in every 15 sudden cardiac deaths and one in eight strokes are associated with the 08.00 to 12.00 hours morning blood pressure surge period [11]. Another study found that people with a strong morning surge have a significantly higher risk of both silent cerebrovascular infarct and clinical stroke (Figure 2) [8]. “It is clearly important that the drugs that we use should reduce blood pressure in a consistent fashion throughout the day,” Prof. McInnes said.

One measure of blood pressure variability is the smoothness index. Smoothness index is the measure of homogeneity of the 24-hour blood pressure control. It is a precise measure, mathematically, it appears to be clinically relevant, and may be a prognostic indicator for target organ damage. The higher the index, the lower the degree of blood pressure variability over 24 hours. Telmisartan has the highest smoothness index of the angiotensin receptor blockers, Prof. McInnes noted. Telmisartan is an insurmountable AT1 receptor blocker, implying that it can maintain its effect even in the presence of high circulating levels of angiotensin II. Its very high affinity and duration of binding with the receptor gives it a high potency, the longest half-life of any ARB and long duration of effect. Because it is highly lipophilic it has a high transmembrane diffusion in tissues, and has the highest volume of distribution of the ARB class. This provides both systemic and local AT1 receptor blockade [14]. Telmisartan is eliminated mainly through the liver, so there is no need for dosage adjustment in patients with renal failure.

“Telmisartan appears to have a profile that is ideal for controlling blood pressure throughout the 24 hours,” Prof. McInnes observed. In a comparison between valsartan and telmisartan using hourly blood pressure readings for 24 hours, the MICADO II study found that telmisartan produced significantly lower blood pressure in the early morning hours (p = 0.02) [15]. A long duration of action is particularly useful in patients who do not take their medication in a regular pattern. A pooled analysis of the MICADO data showed that telmisartan lowered blood pressure significantly more 24 hours after a missed dose than did valsartan (p < 0.001) [16]. Telmisartan also provided more effective lowering in the last six hours of the dosing period after an active dose (p = 0.0066).
Study acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDNT</td>
<td>Irbesartan in Diabetic Nephropathy Trial</td>
</tr>
<tr>
<td>RENAAAL</td>
<td>Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan</td>
</tr>
<tr>
<td>AMADEO</td>
<td>A comparison of telmisartan versus losartan in hypertensive type 2 diabetic patients with Overt nephropathy</td>
</tr>
<tr>
<td>PAMELA</td>
<td>Premiers Arteriostes Monitorates e Loro Associazioni</td>
</tr>
<tr>
<td>MICADO</td>
<td>Micardis missed Dose</td>
</tr>
</tbody>
</table>

References