Key findings of the ADVANCE study

Stephen MacMahon (The George Institute for International Health, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia) presented the key findings of the ADVANCE trial [1–3], reviewing the benefits of fixed-combination perindopril/indapamide in terms of the prevention of both macro- and microvascular events. He primarily focused on the data from the blood pressure-lowering arm [1,3], but gave a quick overview of the glucose-lowering arm findings (Figure 2) [2].

ADVANCE: A new era in diabetes and hypertension

Data from both treatment arms of the ADVANCE trial are now available, with the results of the blood pressure-lowering arm published in the *Lancet* [1] in September 2007 and those from the glucose-lowering arm recently released at the 68th Scientific Sessions of the American Diabetes Association (ADA) and just published in the *New England Journal of Medicine* [2]. It was therefore an opportune time to review data from the trial during the educational symposium entitled ADVANCE: A new era in Diabetes and Hypertension [3]. John Chalmers (The George Institute for International Health, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia) chaired the symposium with Giuseppe Mancia (Department of Clinical Medicine and Prevention, Ospedale San Gerardo dei Tintori, University of Milano-Bicocca, Monza-Milan, Italy).

The ADVANCE study is the largest outcome trial to assess the macro- and microvascular benefits of blood pressure-lowering and intensive glucose control in patients with type 2 diabetes. The study had a 2x2 factorial design (Figure 1) and involved 11,140 patients recruited from 20 countries worldwide.

The blood pressure-lowering arm compared the effects of a fixed combination of the angiotensin-converting enzyme (ACE) inhibitor perindopril and the diuretic agent indapamide on top of standard therapy on major vascular complications versus standard therapy in type 2 diabetes patients, irrespective of initial blood pressure. The glucose-lowering arm compared standard anti-diabetic therapy with intensive therapy that incorporated the sulphonylurea gliclazide MR and aimed to reach a target glycosylated haemoglobin (HbA1c) of ≤6.5%.

**Figure 1**

DESIGN OF THE ADVANCE STUDY

Factorial design

<table>
<thead>
<tr>
<th>Perindopril/indapamide combination</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliclazide MR-based intensive glucose control</td>
<td>Placebo</td>
</tr>
<tr>
<td>Standard guidelines-based intensive glucose control</td>
<td></td>
</tr>
</tbody>
</table>


**Key findings of the ADVANCE study**

Stephen MacMahon presented the key findings of the ADVANCE trial [1–3], reviewing the benefits of fixed-combination perindopril/indapamide in terms of the prevention of both macro- and microvascular events. He primarily focused on the data from the blood pressure-lowering arm [1,3], but gave a quick overview of the glucose-lowering arm findings (Figure 2) [2].
The ADVANCE study was designed to answer two clinical questions highly pertinent at the time the trial began in 2000, said Prof. MacMahon. Those were whether all patients with diabetes would benefit from blood pressure-lowering regardless of their baseline readings and also whether intensive glucose control would improve overall outcomes. The results confirm that intensive glucose control with glaglizide MR is able to safely reduce HbA1c and reduce the overall risk of serious diabetic complications [2]. Importantly, and in contrast to the ACCORD trial [4], no increase in mortality was observed in patients randomised to the intensive glucose-lowering arm.

With regards to the blood pressure-lowering arm, active treatment with a fixed combination of perindopril/indapamide was found to significantly reduce systolic blood pressure by an average of 5.6 mm Hg and diastolic blood pressure by 2.2 mm Hg (p > 0.001) over an average of 4.3 years' follow-up [3] (Figure 3). Most importantly, treatment with the fixed combination of the ACE inhibitor and diuretic resulted in a significant decrease in total mortality, cardiovascular deaths and major vascular events (major macro- or microvascular event combined) [3,3].

Increasing experimental evidence suggests that diabetic complications result from a pathway that starts with glucose-induced damage and oxidative stress or haemodynamic parameters such as blood pressure and vasoactive hormones [5]. In particular, when suppressed, angiotensin II has most clearly been described to reduce the development of diabetic nephropathy. “So agents such as ACE inhibitors have turned out to be very powerful agents in reducing nephropathy,” Prof. Cooper commented.

New data on renal outcomes in the ADVANCE trial show that all patients randomised to perindopril/indapamide benefit in terms of experiencing fewer renal events as compared with placebo, regardless of their baseline blood pressure readings (Figure 5) [6]. These benefits were also observed regardless of in 75, and one renal event, mostly new-onset microalbuminuria, in every 20 patients,” Prof. MacMahon said. He noted that systolic blood pressure lowering below 145 mm Hg does produce additional benefits in patients with diabetes and that similar benefits were observed in hypertensive and non-hypertensive individuals. “Our conclusion is that patients with type 2 diabetes should now be considered routinely for treatment with the combination of an ACE inhibitor and a diuretic.”

**Advanced kidney protection**

One of the most striking findings of the blood pressure-lowering arm of the ADVANCE study was the significant reduction in the total number of renal events. The relative risk of a renal event (new or worsening nephropathy or new microalbuminuria) was 21% lower in patients treated with fixed-combination perindopril/indapamide (Figure 4), a finding discussed in more detail by the next speaker, Mark E. Cooper (Danielle Alberti Memorial Centre for Diabetic Complications, Diabetes and Metabolism Division, Baker Heart Research Institute, Melbourne, Australia). “The ADVANCE study has really taught us that we have the right treatments and approaches now to further reduce the burden of diabetic nephropathy, the commonest cause of end-stage renal failure in Western countries.”

### Key Findings of the Glucose-Lowering Renal Outcomes in the Advance Study 2.0

**Figure 2**

Comparing intensive with standard glucose lowering:

- Mean HbA1c at final visit: 6.5% vs. 7.3%, a 0.67% significant difference (p > 0.0001)
- Fasting plasma glucose decreased by 1.22 mmol/L (21.9 mg/dL) (p < 0.0001)
- 10% RRR in primary composite end point of microvascular and macrovascular events (p = 0.013)
- 14% RRR in major microvascular events (p = 0.015)
- In contrast to ACCORD*, no increase in mortality (7% RRR in all-cause mortality, p = 0.28)

**Figure 3**

Comparing fixed-combination perindopril/indapamide with standard therapy plus placebo:

- Average blood pressure was 134.7/74.8 mm Hg versus 140.3/77.0 mm Hg, a decrease of 5.6/4.2 mm Hg (p > 0.001)
- 14% RRR in all-cause mortality (p = 0.025)
- 18% RRR in cardiovascular death (p = 0.027)
- 9% RRR in major vascular events (p = 0.041)
- 14% RRR in total coronary events (p = 0.02)
- 21% RRR in total renal events (p ≤ 0.01)

### Table: Renal Outcomes in the Advance Study

<table>
<thead>
<tr>
<th>Number of events</th>
<th>Per/Ind (n = 5,569)</th>
<th>Placebo (n = 5,571)</th>
<th>Favours Per/Ind</th>
<th>Favours Placebo</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total renal events</td>
<td>1,243</td>
<td>1,500</td>
<td></td>
<td></td>
<td>21% (15–27%)*</td>
</tr>
<tr>
<td>New or worsening nephropathy</td>
<td>181</td>
<td>216</td>
<td></td>
<td></td>
<td>18% (1–32%)</td>
</tr>
<tr>
<td>New microalbuminuria</td>
<td>1,094</td>
<td>1,317</td>
<td></td>
<td></td>
<td>21% (14–27%)</td>
</tr>
</tbody>
</table>

* 2p ≤ 0.01

Per/Ind = perindopril/indapamide fixed combination; RRR = relative risk reduction; CI = confidence interval

**Figure 4**


**Figure 5**

patient age, gender, duration of diabetes, HbA1c level and whether they had been treated with any previous antihypertensive medications, including ACE inhibitors. There was also a clear linear relationship between the achieved systolic blood pressure and the number of renal events, with patients with the lowest blood pressure reading least likely to experience renal problems.

In the ADVANCE study, the albumin excretion rate was reduced by 42% with perindopril/indapamide as compared with a 27% with placebo, said Prof. Cooper. In the PREMIER trial, the albumin excretion rate was reduced by 42% with perindopril/indapamide as compared with a 27% with placebo, said Prof. Cooper. In the PREMIER trial, the albumin excretion rate was reduced by 42% with perindopril/indapamide as compared with a 27% with placebo, said Prof. Cooper. In the PREMIER trial, the albumin excretion rate was reduced by 42% with perindopril/indapamide as compared with a 27% with placebo.

**Figure 5** MAJOR RENAL OUTCOMES BY BASELINE BLOOD PRESSURE IN THE ADVANCE STUDY

<table>
<thead>
<tr>
<th>Number of events/patient</th>
<th>Per/Ind</th>
<th>Placebo</th>
<th>Favours Per/Ind</th>
<th>Hazards ratio RRR (95% CI) for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>1,241/5,856</td>
<td>1,500/5,569</td>
<td>21% (15–27%)</td>
<td></td>
</tr>
<tr>
<td>Baseline systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120</td>
<td>134/615</td>
<td>167/560</td>
<td>30 (12–44)</td>
<td>0.7</td>
</tr>
<tr>
<td>120–139</td>
<td>367/1,736</td>
<td>431/1,793</td>
<td>15 (3–26)</td>
<td></td>
</tr>
<tr>
<td>140–159</td>
<td>439/1,945</td>
<td>563/2,003</td>
<td>25 (15–34)</td>
<td></td>
</tr>
<tr>
<td>≥160</td>
<td>303/1,273</td>
<td>339/1,215</td>
<td>19 (5–30)</td>
<td></td>
</tr>
<tr>
<td>Baseline diastolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>208/846</td>
<td>240/881</td>
<td>168(2–30)</td>
<td>0.85</td>
</tr>
<tr>
<td>70–79</td>
<td>387/1,748</td>
<td>481/1,758</td>
<td>23(12–33)</td>
<td></td>
</tr>
<tr>
<td>80–89</td>
<td>386/1,862</td>
<td>479/1,834</td>
<td>24(13–34)</td>
<td></td>
</tr>
<tr>
<td>≥90</td>
<td>262/1,113</td>
<td>300/1,098</td>
<td>10(4–31)</td>
<td></td>
</tr>
</tbody>
</table>

Importantly, these new data also show that adding perindopril/indapamide not only reduced progression of albuminuria by 22% compared with standard therapy, but also was associated with significant regression of albuminuria (Figure 6). As such, these new data from the ADVANCE study build on those of the PREMIER trial, said Prof. Cooper. In the PREMIER study, the albumin excretion rate was reduced by 42% with perindopril/indapamide as compared with a 27% with enalapril (p < 0.001) [7]. There was also a greater reduction in progression of albuminuria in the ADVANCE study, perindopril/indapamide reduced progression of albuminuria by 22% compared with standard therapy, but also was associated with significant regression of albuminuria (Figure 6). As such, these new data from the ADVANCE study build on those of the PREMIER trial, said Prof. Cooper. In the PREMIER study, the albumin excretion rate was reduced by 42% with perindopril/indapamide as compared with a 27% with enalapril (p < 0.001) [7].

In the ADVANCE study, the risks associated with macro- and microalbuminuria at baseline were end-stage renal disease (ESRD), macrovascular events (e.g., myocardial infarction), cardiovascular death and total mortality. These risks were expectedly higher in patients with macroalbuminuria at baseline as compared with those without microalbuminuria at baseline. ESRD was present in 3.4% of patients with macroalbuminuria at baseline (n = 404) and 0.3% of those without; respective values for macrovascular events, cardiovascular death and all-cause mortality in patients who had microalbuminuria at baseline (n = 2,857) compared with those who did not (n = 8,282).

Prof. Cooper concluded: “I think in type 2 diabetic patients, to confer optimal renoprotection, we have to use not only a multifactorial approach involving aggressive blood pressure-lowering but also, importantly, we now have the data that intensified glycaemic control is a very important approach to reduce renal events in type 2 diabetes.”

**Shielding the heart from hypertension**

Paolo G. Camici (Medical Research Council Clinical Sciences Centre and National Heart and Lung Institute, Imperial College, London, UK) discussed how perindopril/indapamide may affect the coronary microcirculation, and how this could in turn offer protection against cardiac events as seen in the ADVANCE trial. Hypertension and diabetes are the most common risk factors for coronary events, he said, noting that together these two risk factors account for 68% of all cardiovascular events that occur worldwide. In the ADVANCE study, perindopril/indapamide reduced cardiovascular mortality by 18%, total coronary events by 14%, and total renal events by 21%, he said, but what could be the underlying reason these beneficial effects were observed?

The coronary circulation consists of three components, Prof. Camici explained. These are the epicardial coronary arteries, the prearterioles, and the arterioles, with the latter two components making up the microcirculation [8,9]. The function of these vessels is to ensure that the blood supply and oxygen consumption of the heart are in sync. The concept of coronary microvascular dysfunction is relatively recent [8,9], and may occur in the absence of major coronary artery disease. Problems with the larger arteries are just the “tip of the iceberg,” he suggested, noting that it is well accepted that coronary stenosis caused by atherosclerosis is linked to poor patient outcomes and survival.
Abnormalities in the structure and function of the coronary microcirculation have been shown to cause myocardial ischaemia and occur in patients with arterial hypertension and left ventricular hypertrophy (LVH), with subsequent effects on cardiovascular morbidity and mortality. It is thought that dysfunction of the microcirculation could be due to remodelling of vascular and extravascular structures, as well as abnormal haemodynamics.

Prof. Camici reported that fixed-combination perindopril/indapamide had been shown to reduce left ventricular hypertrophy (LVH) to a greater extent than enalapril alone, and that this had led to a study examining the effects of the combination specifically on the coronary microcirculation. Preliminary data from this study, reported at last years’ ESH [10], had shown that SIX months’ treatment with the combination had led to a significant decrease in systolic and diastolic blood pressure, left ventricular mass, and myocardial blood flow. These results suggest a “reverse remodelling of coronary arterioles.”

Prof. Camici concluded: “I believe that the benefits of the combination on cardiac remodelling as well as myocardial perfusion could explain the coronary events and cardiovascular mortality reduction that was observed in the ADVANCE study.”

**ADVANCE data add to evidence-based guidelines**

It is never too little or too late to control blood pressure in patients with type 2 diabetes, said Luis M. Ruilope (Hypertension Unit, Hospital 12 de Octubre, Complutense University of Madrid, Madrid, Spain). Dr. Ruilope looked at the findings from the ADVANCE study in relation to the current ESH guidelines for the control of blood pressure in patients with diabetes [11]. These guidelines base treatment for hypertensive patients on their risk of developing cardiovascular disease, stratified according to their level of hypertension and the presence of additional risk factors. Diabetes and hypertension are both established risk factors for cardiovascular disease and antihypertensive therapy is indicated in addition to lifestyle changes when both factors are present. “The combination of diabetes and hypertension is the most devastating combination that you can find in daily clinical practice,” said Dr. Ruilope. As soon as the systolic blood pressure exceeds 130 mm Hg in a patient with diabetes, pharmacological intervention is necessary. The accepted threshold for systolic blood pressure in non-diabetic patients at which treatment should be given is 140 mm Hg.

The guidelines were published before the ADVANCE data were available but recommend that all effective and well-tolerated drugs should be used, including combinations of drugs if needed. Intensive lifestyle changes, such as reduction of salt and decreasing body weight, are always suggested and renal protection in diabetes requires suppression of the renin–angiotensin system (RAS). This should be a routine component of combination therapy and the preferred option when monotherapy is all that is required, said Dr. Ruilope. Statin therapy should also be considered.

The ADVANCE data, showing the multiple benefits of the perindopril/indapamide combination in patients with diabetes, confirm and add to the guideline recommendations of using combination therapy when diabetes and hypertension coexist. They also confirm the need for early intervention of the combination, said Dr. Ruilope.

**Managing very elderly hypertensive patients**

“You are never too old to start treatment for hypertension,” said Bryan Williams (Leicester Royal Infirmary, Leicester, UK), who chaired the symposium discussing the HYVET study. The trial, which was conducted in an often-neglected age group of patients aged 80 years and older, clearly is a landmark trial, he said, emphasising that age should not be a barrier to initiating antihypertensive therapy. “There is no doubt that in this age group a diuretic is the most appropriate therapy to reduce blood pressure,” he said. ESH President Stéphane Laurent (Department of Pharmacology, Hôpital Européen Georges Pompidou, Paris University Descartes, Paris, France), who co-chaired the session, agreed. He added that the findings from the HYVET study fill the gap between clinical practice and currently available guidelines. “We know that prescribing indapamide SR 1.5 mg with or without perindopril will reduce, by 30%, fatal and non-fatal stroke, cardiovascular mortality by 23%, and heart failure by 64%,” he said, citing just some of the key findings of the study. The results also showed that total mortality was reduced by 21% in those treated with the diuretic with or without the ACE inhibitor.

**Increasing age, increasing blood pressure**

Françoise Forette (Department of Geriatrics, Hôpital Broca, Paris University Descartes, Paris, France) added her thoughts as to why HYVET is such an important study. The very elderly are “the most rapidly growing segment of the population,” she said and are at high risk of cardiovascular disease, stroke, and dementia. They also have high rates of concomitant disease such as diabetes, arthritis, osteoporosis and malignancies. There is no doubt that the incidence of hypertension increases with age. Indeed, data show that over 70% of both men and women aged 80 years and older are clinically hypertensive and require treatment. However, even when treated, blood pressure is only adequately controlled in around 10–20% of very elderly individuals.

Prior to the HYVET trial, it was not known if blood pressure was still an important risk factor for cardiovascular disease in the very elderly. Only a few small, observational epidemiological studies had shown a positive correlation between increasing blood pressure and survival, and larger placebo-controlled trials had included too few elderly patients ≥80 years of age to be able to draw any firm conclusions. Dr. Forette noted that, somewhat paradoxically, some of the studies had shown that the higher the blood pressure, especially diastolic blood pressure, the longer the survival. Prof. Williams noted elsewhere during the symposium that it was the systolic blood pressure that clinicians should be
worried about, not the diastolic [13]. Thus, before the HYVET trial, the benefits of routine use of antihypertensive therapy in very elderly patients in terms of cardiovascular disease prevention were not clear and many experts worried about the possible side effects of treatment, as well as giving a therapy that had no proven benefits on overall mortality. As such the HYVET data were eagerly awaited.

**Hypertension linked to dementia**

“Hypertension is not just a risk factor for cardiovascular disease, but also for dementia,” Dr. Forette commented. Prior investigations had shown a positive association between hypertension and vascular dementia, but the possible link to other forms of cognitive dysfunction, such as Alzheimer’s disease, were less clear. New data on the cognitive function of patients enrolled in the HYVET study were presented during a late-breaking poster session at the ESH meeting and are discussed below, and these appear to add to the existing body of evidence that treating hypertension helps decrease the likelihood of cognitive decline.

Concluding, Dr. Forette noted that at the time the HYVET study was conceived, there was uncertainty if there was an age at which hypertension should not be treated. The lack of data on what effect treatment may have on survival was used as a reason to abstain from treating, even though some evidence suggested that treatment may preserve quality of life by preventing distressing and disabling conditions, such as cognitive dysfunction.

**HYVET: large investigation in very elderly**

The HYVET study was a unique undertaking involving 3,845 very elderly (>80 years) patients. The study rationale, design and study population were reviewed by Krzysztof Narkiewicz (Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland). He noted that, years ago, living past 80 years of age was the exception and not the rule, whereas today it has become more commonplace. Indeed, the United Nations have estimated that in 2000, the year before the HYVET trial was started, there were 69.2 million people over the age of 80 around the world. They also estimated that the number of very elderly individuals in the world population would more than double by 2025, and reach a staggering 379 million by 2050. Prof. Narkiewicz noted that age is a major risk factor for fatal stroke, heart failure is a common finding in elderly patients, and that the EWPHE, STOP-H, SHEP and Syst-Eur trials had shown conflicting results as to the benefits of antihypertensive therapy over the age of 80 years. Prior to HYVET, hypertension guidelines gave little or no direction on how to treat patients over the age of 80 years. This is still the case, but the HYVET study findings are likely to influence changes in guidelines recommendations, it was later noted by Prof. Williams.

HYVET was an international trial conducted in patients recruited from Europe, China, Australasia and Tunisia. Almost two thirds (60%) of the study population were female, and to be included, all had to have a baseline systolic blood pressure of 160–199 mm Hg and a diastolic blood pressure of <100 mm Hg. Prof. Narkiewicz noted that the mean baseline blood pressure was 173.0/90.8 mm Hg and that the aim had been to reduce this down to below 150/80 mm Hg. Patients were randomised to one of two study arms: indapamide SR at a daily dose of 1.5 mg (n = 1,933) or placebo (n = 1,921), and the median follow-up was for 1.8 years (mean 2.2 years). The primary end point was all strokes (fatal and non-fatal), with secondary end points being total mortality, cardiovascular mortality, cardiac mortality, stroke mortality and heart failure. Just under 90% of the recruited patients had known hypertension at baseline, and two thirds were receiving treatment. The patients were, however, somewhat healthier than the general elderly population, with around 12% having previous cardiovascular disease, <7% having had a stroke or diabetes, and ≤3% having a prior myocardial infarction or heart failure.

**Key findings from HYVET**

The HYVET study results were announced at the 57th Scientific Sessions of the American College of Cardiology in March 2008, and published rapidly online in the *New England Journal of Medicine* [13] to coincide with their presentation. Christopher J. Bulpitt, emeritus professor at the Division of Medicine, Imperial College, London, UK, outlined the key findings of the trial during the symposium at Hypertension 2008 (Figure 7) and discussed their implications. He noted that the HYVET study was stopped early because of a 21% reduction in total mortality (Figure 8) and significantly fewer strokes occurring in patients treated with indapamide versus placebo. In addition, “there was an enormous reduction in heart failure, at least 64%,” (Figure 9) said Prof. Bulpitt.

![Figure 7](image-url)  
**KEY FINDINGS OF THE HYVET STUDY**

Comparing indapamide SR 1.5 mg with placebo after a median follow-up of 1.8 years (mean 2.2 years):

- 15.0/6.0 mmHg average decrease in blood pressure
- 30% reduction in all strokes (fatal and non-fatal) \( p = 0.055; \) 95% CI (0.49–1.01)
- 39% reduction in death from stroke \( p = 0.046; 95\% \text{ CI} \ (0.38–0.99)\)
- 21% reduction in total mortality \( p = 0.019; 95\% \text{ CI} \ (0.65–0.95)\)
- 23% reduction in death from cardiovascular causes \( p = 0.06; 95\% \text{ CI} \ (0.60–1.01)\)
- 29% reduction in death from cardiac causes \( p = 0.19; 95\% \text{ CI} \ (0.42–1.19)\)
- 64% reduction in heart failure \( p < 0.0001; 95\% \text{ CI} \ (0.22–0.58)\)
- Fewer serious adverse events

CI = confidence interval


Data presented from the study are usually from the intention-to-treat analysis and the results of the per protocol analysis are seldom discussed. However, the per protocol data show clearly that the findings of the trial are robust. When a per protocol analysis was performed, meaning that the study population included only those patients who had received the allocated treatment, the reductions noted in total stroke, total mortality,
Cardiovascular and stroke deaths, and heart failure all remained significantly in favour of treatment with indapamide ± perindopril (Figure 10). Furthermore, said Prof. Bulpitt, new data from subgroup analyses of the trial being presented at Hypertension 2008 show that the results are in favour of lowering blood pressure with indapamide ± perindopril in the elderly regardless of whether the patient is male or female or has pre-existing or no cardiovascular disease (Figure 11) [14].

There are also new data available from a substudy of HYVET looking at cognitive function in relation to blood pressure [15].

What are the implications of HYVET for everyday practice?

Prof. Bulpitt noted that treating 40 patients for two years with indapamide ± perindopril would save one life, with 94 patients needing to be treated to prevent one stroke and 50 patients in order to prevent one person from developing heart failure. A couple of caveats should be considered when looking at these data, notably that the HYVET patient population was relatively healthy compared with the general population. Furthermore, there were relatively few patients aged over 90 years and the benefits of treating patients with systolic blood pressures less than 160 mm Hg at the start remains to be determined, as does investigating if there is any benefit of lowering blood pressure below the target of 150/80 mm Hg used in this study.

Prof. Williams noted that until now guidelines have remained understandably cautious about the treatment of hypertension in the very elderly but that these new data from the HYVET study certainly had the potential to be practice-changing. “The results of HYVET are unequivocal,” he said. “Lowering blood pressure in the very elderly with the treatment strategy deployed in this trial was very safe and very effective.” A simple intervention is all it takes to significantly improve the clinical outcomes of more elderly patients. “HYVET has removed the uncertainty about the benefits of treating high blood pressure in the very elderly,” added Prof. Williams and “will clarify and change, I think, the international guidelines.”

New data from HYVET: subgroups analyses

The benefits of lowering high blood pressure in patients aged 80 years or older with the diuretic indapamide with or without cardiovascular and stroke deaths, and heart failure all remained significantly in favour of treatment with indapamide ± perindopril (Figure 10). Furthermore, said Prof. Bulpitt, new data from subgroup analyses of the trial being presented at Hypertension 2008 show that the results are in favour of lowering blood pressure with indapamide ± perindopril in the elderly regardless of whether the patient is male or female or has pre-existing or no cardiovascular disease (Figure 11) [14].

There are also new data available from a substudy of HYVET looking at cognitive function in relation to blood pressure [15].

**Figure 10** PER PROTOCOL DATA SHOW HYVET FINDINGS ARE ROBUST

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>p</th>
<th>PP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke</td>
<td>−30%</td>
<td>0.06</td>
<td>−34%</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke mortality</td>
<td>−21%</td>
<td>0.02</td>
<td>−28%</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>−39%</td>
<td>0.05</td>
<td>−45%</td>
<td>0.02</td>
</tr>
<tr>
<td>Heart failure</td>
<td>−64%</td>
<td>&lt;0.001</td>
<td>−72%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>−34%</td>
<td>&lt;0.001</td>
<td>−37%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ITT = intention to treat; PP = per protocol


**Figure 11** SUBGROUP ANALYSIS SHOWS BENEFIT ON INDAPAMIDE REGARDLESS OF GENDER OR PRESENCE OF CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th></th>
<th>Total mortality HR (95% CI)</th>
<th>Cardiovascular events HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1,519</td>
<td>0.82 (0.62–1.11)</td>
</tr>
<tr>
<td>Women</td>
<td>2,326</td>
<td>0.77 (0.66–0.99)</td>
</tr>
<tr>
<td>History of CVD</td>
<td>452</td>
<td>0.76 (0.48–1.20)</td>
</tr>
<tr>
<td>No history of CVD</td>
<td>3,393</td>
<td>0.81 (0.65–0.99)</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval

additional perindopril are consistently observed, the results of subgroup analyses of the HYVET data show (Figure 11) [14]. Nigel S. Beckett (Division of Medicine, Imperial College, London, UK) presented these data during a late-breaking poster session at Hypertension 2008. He commented: “The subgroups analyses suggest that the benefits found in HYVET apply to both men and women, those under 85 and those 85 or over, and irrespective of whether subjects have established cardiovascular disease or not.” Benefits were also seen regardless of patients’ initial systolic blood pressure. Dr. Beckett and colleagues reported that for both total mortality and total cardiovascular events, “statistically significant benefits or positive trends” were seen for the four subgroups studied. “This adds further support for the treatment of all very elderly hypertensives,” they concluded.

Results of cognitive dysfunction substudy

Data from the cognitive dysfunction substudy of HYVET add to existing evidence that treating hypertension can decrease the risk of dementia. Ruth Peters (Division of Medicine, Imperial College, London, UK) presented the findings during the late-breaking poster session at Hypertension 2008. HYVET-COG involved 3,336 of the main study cohort, of whom 1,687 received active therapy with indapamide with or without perindopril. Patients’ cognitive function was assessed at randomisation using the Mini-Mental State Examination (MMSE), which was repeated annually. If any patients’ MMSE score fell from ≥24 to <24 they were flagged for further evaluation, and anyone whose score fell by more than three points over the course of any one year was also assessed more fully. Dementia was assessed using standard methods, including Diagnostic Statistical Manual edition IV (DSM-IV) criteria and computed tomography.

MMSE scores fell by a mean of 0.7 in the active treatment group and by 1.1 in the placebo group, although this difference was not statistically significant (p = 0.08). In total, 263 cases of dementia were diagnosed, of which 84 were vascular dementia and 164 were Alzheimer’s disease. Other subtypes of dementia could not be specified in the remaining 15 patients. The rate of incident dementia was lower in the active-treatment group compared with placebo, at 33 and 38 cases per 1000, respectively. Looking at the specific subtype of dementia did not yield any significant results. “The HYVET results for the evaluation of dementia incidence are in line with other earlier trials in younger subjects,” Ms. Peters said. Furthermore, “when combined with these trials, these new findings reinforce the potential role of antihypertensive treatment in the prevention of dementia.”
Trial acronyms

ACCORD  Action to Control Cardiovascular Risk in Diabetes
ADVANCE  Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation
EWPH  European Working Party on High Blood Pressure in the Elderly
HYVET  Hypertension in the Very Elderly
SHEP  Systolic Hypertension in the Elderly Program
Syst-Eur  Systolic Hypertension in Europe Trial
STOP-H  Swedish Trial in Old Patients with Hypertension

References