Dihydropyridine calcium-channel blockers for the treatment of hypertensive diabetic patients

Introduction
Diabetes mellitus and hypertension are commonly associated conditions. The prevalence of hypertension in type 2 diabetes is higher than in the general population. At the age of 45 around 40% of patients with type 2 diabetes are hypertensive, the proportion rising to 60% by the age of 75[1]. Hypertension potentiates the already high risk of cardiovascular complications associated with diabetes mellitus.

In 1997, the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure recommended the use of angiotensin-converting enzyme inhibitors, alpha-blockers, calcium-channel blockers or low-dose diuretics[2] to initiate antihypertensive drug treatment in hypertensive diabetic patients[3]. In patients with diabetic nephropathy, angiotensin-converting enzyme inhibitors were proposed as the first-line treatment[3]. At variance with these guidelines, two studies published in 1998 raised major concerns about the use of dihydropyridines in diabetic patients[4,5]. Subsequent papers published in 1998[6] and 1999[7–9], based on larger numbers of patients, demonstrated that long-acting calcium-channel blockers are not only safe to use in diabetic patients, but that they may even confer particular benefit to this important subgroup of the hypertensive population. These recent studies are shortly reviewed (Table 1) and put into perspective.

How accurate was the alarming news?
The primary purpose of the Appropriate Blood Pressure Control in Diabetes (ABCD) Trial[4] was to compare progression of diabetic nephropathy, under treatment with the converting-enzyme inhibitor enalapril or the calcium-channel blocker nisoldipine. All 480 normotensive and 470 hypertensive patients were randomized. Patients with hypertension always received active study medication and were randomized to either nisoldipine (10–60 mg per day) plus enalapril–placebo or enalapril (5–40 mg per day) plus nisoldipine–placebo. The drugs and placebos were administered in a double-blind manner. After 67 months of study, the Data and Safety Monitoring Committee observed a significant difference in the rate of myocardial infarction between the subgroups of patients treated with the two study drugs in the hypertensive cohort only (relative risk of nisoldipine vs enalapril: 5·5; number of myocardial infarctions: 25 vs 5). On the basis of this information, the committee recommended the discontinuation of nisoldipine therapy among the patients with hypertension and the continuation of blinded therapy among the normotensive patients.

The results of the ABCD trial[6] require careful interpretation. The decision to prematurely stop the trial and to report a secondary end-point only in the hypertensive subgroup is open to criticism. In an era of controversy, the Data and Safety Monitoring Committee may have had its attention focused on an extreme result that was not prespecified, not subject to monitoring boundaries, and for which the trial was not powered, thus inflating the chance of a false positive finding. Treatment status and doses of the double-blind study medication at the time of the myocardial infarctions were also not reported. Because more diuretics (119 vs 93; P=0·02) and beta-blockers (95 vs 89; P=0·04) were prescribed in the enalapril group, and because the active study medication was stopped more frequently in the nisoldipine group (142 vs 129; P=0·022), overall, cardiovascular protection may have been unbalanced in favour of the enalapril group. In view of the high drop-out rate a per-protocol analysis should have been presented. Any cardiovascular event may be the harbinger of myocardial infarction. For this reason, a first-ever-event analysis would also have been helpful for the correct interpretation of the ABCD results, but was not reported.

The Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) was an open-label randomized study in patients with hypertension and type 2 diabetes[5]. Its primary goal was to assess treatment-related differences in serum lipids, diabetes control and renal function. Patients were randomly assigned to receive fosinopril (20 mg per day) or amlodipine (10 mg per
day) as the first-line drug. If blood pressure remained beyond control, the alternative drug was added to the initial regimen. FACET was first presented as a poster at the 56th Meeting of the American Diabetes Association (San Francisco, June 8–11 1996). The five Italian authors showed the results in three groups of patients, treated respectively with amlodipine (n=140), fosinopril (n=130), or both drugs (n=110). The analysis was restricted to the occurrence of morbid cardiac events, defined as well documented acute myocardial infarctions and new-onset angina pectoris. In the intention-to-treat analysis, there were 17 such events in the amlodipine group (n=140), seven in the fosinopril group (n=130) and three in patients on combined treatment (n=110). The investigators were struck by the low number of major cardiac events seen with the association of amlodipine and fosinopril (P=0.006) and suggested that the combination of an angiotensin-converting enzyme inhibitor and a calcium-channel blocker would be a rational therapeutic approach to hypertensive patients, especially if diabetic.

The Italian and American authors of the definite FACET report recognized that their trial was not designed and powered to assess a difference between the two treatments in vascular events and that the open-label and single-site design with a 6-month interval between the visits was not ideal. Events had been monitored by ‘asking’ patients if they had been hospitalized or had experienced any other event. The final report clarified that the patients had been assigned to treatment by a computer-generated random number sequence obtained from an investigator who was not involved in patient recruitment. Furthermore, the trial was now analysed based on the two randomized groups. The diagnostic criteria were apparently revised so that end-points other than morbid cardiac events were considered in the analysis. Using the intention-to-treat approach, the patients receiving fosinopril had a significantly lower risk of the combined outcome of acute myocardial infarction, stroke, or hospitalized angina pectoris than those receiving amlodipine (14/189 vs 27/191 events). In contrast to the poster report and the ABCD trial findings[4], the worse outcome on amlodipine compared with fosinopril was not only due to myocardial infarction (13 vs 10), but was driven by hospitalized angina (4 vs 0) and stroke (10 vs 4). The interpretation of these findings also remains clouded by the fact that 58 patients randomized to fosinopril (30.7%) and 50 of the amlodipine group (26.2%) crossed over and received the combination of both drugs (108 patients in the definite report vs 110 in the poster presentation). In addition, microalbuminuria at entry averaged (SE) 24±1 μg min⁻¹ in the amlodipine group and 20±1 μg min⁻¹ in the fosinopril group (P<0.05). This difference may well have been of importance, because in type 2 diabetic patients the accuracy of microalbuminuria in predicting cardiovascular morbidity and mortality is at least as great as that of cholesterol, hypertension, smoking, and even pre-existing coronary artery disease.

**Evidence from large placebo-controlled trials**

In the Systolic Hypertension in Europe (Syst-Eur) trial, 4695 older (≥60 years) patients with isolated
systolic hypertension were randomized to active treatment or placebo. Active treatment was initiated with nitrrendipine (10–40 mg per day). If necessary to achieve blood pressure control, the dihydropyridine was combined with or replaced by enalapril (5–20 mg per day), hydrochlorothiazide (12.5–25 mg per day), or both drugs. Active treatment reduced the total stroke rate from 13.7 to 7.9 events per 1000 patient-years (−42%; \( P=0.003 \)). Non-fatal stroke alone decreased by 44% (\( P=0.007 \)). In the active treatment group, all fatal and non-fatal cardiac end-points, including sudden death, declined by 26% (\( P=0.03 \)). Non-fatal cardiac end-points decreased by 33% (\( P=0.03 \)). Similar trends were observed for non-fatal heart failure (−36%; \( P=0.06 \)), for all cases of heart failure (−29%; \( P=0.12 \)) and for fatal and non-fatal myocardial infarction (−30%; \( P=0.12 \)). Active treatment reduced all fatal and non-fatal cardiovascular end-points by 31% (\( P<0.001 \))\(^{10}\).

Recently, the Syst-Eur investigators published a subgroup analysis focusing on the 492 (10.5%) patients with diabetes mellitus at enrolment\(^{7}\). At entry a significantly higher proportion of diabetic patients reported use of antihypertensive drugs (61.8% vs 44.8%) or had experienced cardiovascular complications (35.0% vs 29.3%). After a median follow-up of 2 years, systolic/diastolic blood pressure decreased to a similar extent in diabetics and non-diabetics by −8.6/−3.9 mmHg and −10.3/−4.6 mmHg, respectively (estimates corrected for placebo effects). Nevertheless, the benefits in preventing end-points were considerably greater in diabetic than in non-diabetic patients (Fig. 1). Indeed, Cox regression with adjustments applied for sex, previous cardiovascular complications, age, systolic blood pressure at entry, smoking habits, and residence in western Europe, showed that in the diabetic patients active treatment reduced total mortality by 55%, cardiovascular mortality by 76%, all cardiovascular end-points by 69%, fatal and non-fatal stroke by 73% and all cardiac end-points by 63%. In the non-diabetic group, active treatment significantly decreased all cardiovascular end-points (−26%) and fatal and non-fatal stroke (−38%). In diabetic patients, compared with the non-diabetics, active treatment had a significantly greater effect on total and cardiovascular mortality and on all cardiovascular end-points combined (\( P=0.04 \), \( P=0.02 \), \( P=0.01 \), respectively).

The Systolic Hypertension in the Elderly Program (SHEP)\(^{2}\) and the Syst-Eur trial\(^{7–10}\) were similar in design and size. However, in the SHEP trial, active treatment was based on chlorthalidone (12.5–25 mg per day) with the possible addition of atenolol (25–50 mg per day) or reserpine (0.05–0.1 mg per day). Using the same end-point definitions as in the SHEP trial and similar adjustments for possible confounders, the Syst-Eur investigators compared their outcome results\(^{7}\) with those observed in SHEP\(^{2}\).

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**Figure 1** Relative hazard rates of active treatment vs placebo in diabetic and non-diabetic patients with cumulative adjustments for sex, age, previous cardiovascular complications, systolic blood pressure at entry, smoking, and residence in western Europe. \( P \) values refer to the treatment-by-diabetes interaction and indicate whether the treatment effect was significantly different according to the presence of diabetes at randomization. Reproduced with permission\(^{7}\). *For interaction between active treatment and diabetes.

![Figure 1: Relative hazard rates](image_url)
**Evidence from other trials**

The Hypertension Optimal Treatment (HOT) study confirmed the evidence on the interaction between calcium-channel blockade and diabetes in hypertensive patients. A total of 18,790 hypertensive patients from 26 countries (mean age: 61.5 years) were randomized to reach one of three target levels of diastolic blood pressure (< 90, ≤ 85 or ≤ 80 mmHg). The calcium-channel blocker felodipine served as the mainstay of treatment (5–10 mg per day) with the possible addition of angiotensin-converting enzyme inhibitors or beta-blockers. The actual blood pressure levels attained in the three groups were 143/78±2 mmHg, 141/48±3 mmHg and 139/71±1 mmHg, respectively. In the study population at large, these small 2 mmHg differences in mean blood pressure at baseline, electrocardiographic abnormalities (SHEP) or previous cardiovascular complications (Syst-Eur) at baseline, and race (SHEP) or residence in western Europe (Syst-Eur).

**Table 2 Results of the Systolic Hypertension in the Elderly Program (SHEP) and the Systolic Hypertension in Europe Trial (Syst-Eur) in diabetic and non-diabetic patients**

<table>
<thead>
<tr>
<th></th>
<th>Diabetics</th>
<th>Non-diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>590 (12.3)</td>
<td>4149 (87.7)</td>
</tr>
<tr>
<td>Mean blood pressure reduction*</td>
<td>492 (10.5)</td>
<td>4203 (89.5)</td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>−9.8</td>
<td>−12.5</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>−2.2</td>
<td>−4.1</td>
</tr>
<tr>
<td>Risk in placebo group†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total mortality</td>
<td>35.6</td>
<td>21.8</td>
</tr>
<tr>
<td>Cardiovascular end-points</td>
<td>63.0</td>
<td>36.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>28.8</td>
<td>15.0</td>
</tr>
<tr>
<td>Coronary events</td>
<td>32.2</td>
<td>15.2</td>
</tr>
<tr>
<td>Change with active treatment (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>−26 (−54, 18)</td>
<td>−15 (−32, 6)</td>
</tr>
<tr>
<td>All cardiovascular end-points</td>
<td>−34 (−54, 6)</td>
<td>−34 (−45, −21)</td>
</tr>
<tr>
<td>Stroke</td>
<td>−22 (−55, 34)</td>
<td>−38 (−54, −17)</td>
</tr>
<tr>
<td>Coronary events</td>
<td>−56 (−75, −23)</td>
<td>−19 (−38, 5)</td>
</tr>
</tbody>
</table>

*The mean effect of active treatment on blood pressure was corrected for baseline and placebo.
†Rate expressed as events per 1000 patient-years.
‡The changes with active treatment were calculated by Cox regression with adjustments applied for sex, age, smoking, systolic and diastolic blood pressure at baseline, electrocardiographic abnormalities (SHEP) or previous cardiovascular complications (Syst-Eur) at baseline, and race (SHEP) or residence in western Europe (Syst-Eur).

The validity of these comparisons is sustained by similar net decreases in blood pressure in the active treatment groups, by similar rates in the placebo groups of the two trials, regardless of the presence of diabetes at randomization, and by the almost identical relative benefit in terms of outcome in the non-diabetic subpopulations. The major difference between the two trials was in the outcome of the diabetic patients, in whom dihydropyridine-based antihypertensive treatment reduced cardiovascular complications and total cardiovascular mortality much more efficaciously than therapy starting with a thiazide diuretic compared with chlorthalidone treatment. At the end of the SHEP trial, 44% of the patients randomized to placebo were on active antihypertensive drugs. However, this does not explain the reduced protection conferred by diuretic-initiated treatment in the diabetic patients, because crossing-over to active treatment should have affected outcome in diabetic as well as non-diabetic patients.

The Syst-Eur findings in diabetic and non-diabetic patients were recently confirmed by a subgroup analysis of the placebo-controlled Systolic Hypertension in China (Syst-China) trial. Of 2394 Syst-China patients, 98 had diabetes (4.1%). On nifedipine (10–40 mg per day) with the possible addition of captopril (12.5–50 mg per day) and/or hydrochlorothiazide (12.5–50 mg per day), the net placebo-subtracted differences in blood pressure after 2 years were −6.0/−4.7 mmHg in the diabetic patients, and −9.3/−3.1 mmHg in the non-diabetics. With adjustment for possible confounders, active treatment decreased the relative risk in diabetic and non-diabetic patients as follows: −59% vs −36% for total mortality, −57% vs −33% for cardiovascular mortality, and −74% vs −34% for all cardiovascular end-points. However, because of the small number of diabetic patients, the diabetes-by-treatment interaction terms were not statistically significant. Nevertheless, active treatment reduced the excess cardiovascular mortality and morbidity observed in the diabetic patients to a non-significant level.
diastolic blood pressure did not influence the incidence of end-points, with the exception of myocardial infarction \((P=0.05)\). In contrast, the subgroup of diabetics \((8\%)\) fared particularly well on having their diastolic blood pressure tightly controlled by felodipine as the main component of the therapeutic regimen. Indeed, the risk of cardiovascular events and cardiovascular mortality was two to three times higher in the patients whose target diastolic blood pressure was 90 mmHg, as compared with those randomized to attain 80 mmHg.

In the context of the ABCD results\(^4\), the decisions taken by the monitoring board of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) may be informative. ALLHAT compares a calcium-channel blocker (amlodipine), an angiotensin-converting enzyme inhibitor (lisinopril) and an alpha-adrenergic-receptor blocker (doxazosine) with a diuretic (chlorthalidone) for effects on the risk of non-fatal myocardial infarction or fatal coronary heart disease among high-risk patients with hypertension who are older than 55 years\(^{11}\). At the time of the ABCD publication\(^4\), nearly 40,000 patients had been randomized, of whom one third had diabetes\(^{11}\). ALLHAT’s Data and Safety Monitoring Board reviewed the outcome data during the autumn of 1997 and included a separate evaluation of the primary end-point in the subgroup with diabetes\(^{11}\). This analysis involved more than 7000 patient-years. According to expected event rates, about three times as many myocardial infarctions should have been observed as in the ABCD trial\(^4\). The ALLHAT committee recommended that the trial continue according to the protocol and did not accelerate the date of its new review of the data\(^6\).

**Conclusions and direction of future research**

The Syst-Eur trial\(^7\) demonstrated that dihydropyridine-based antihypertensive treatment is particularly beneficial in older diabetic patients with isolated systolic hypertension; at the risk observed in the placebo group, treating 1000 patients for 5 years could prevent 178 major events in the diabetic patients and 39 in the non-diabetics. The findings in the Syst-China trial were in line with those in Syst-Eur\(^9\).

The mechanisms underlying the benefit of calcium-channel blockers in diabetic patients remain speculative and may include the absence of metabolic side-effects, such as glucose intolerance and perturbations of the serum lipid profile, renal protection, anti-oxidant effects and a beneficial influence on the flow characteristics of the blood and on endothelial function. Recently, the UK Prospective Diabetes Study (UKPDS)\(^{11}\) demonstrated the importance of tight blood pressure control in hypertensive patients with type 2 diabetes. After a median follow-up of 8.4 years, mean blood pressure in the tight control group was 144/82 mmHg vs 154/87 mmHg in the less controlled group \((P=0.0001)\); statistically significant benefits in the former group included 24% fewer diabetes-related end-points, 32% fewer deaths related to diabetes, and 44% fewer strokes. In view of the latter findings, further prospective studies are required to investigate whether long-acting dihydropyridines, over and above their blood pressure lowering effect, may provide additional cardiovascular and renal protection in hypertensive diabetic patients. ALLHAT is due to report in 2002 and will probably be a cornerstone in the evidence yet to be generated\(^{9,11}\).

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**References**


