Original Article

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Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients

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Abstract

Background. Hypertensive haemodialysis patients may be at a high risk for cardiovascular events. This study was undertaken to ascertain whether the calcium channel blocker amlodipine reduces mortality and cardiovascular events in these high-risk patients.

Methods. We evaluated the effects of amlodipine on cardiovascular events in 251 hypertensive haemodialysis patients in an investigator-designed, prospective, randomized, double-blind, placebo-controlled, multicenter trial. One hundred and twenty-three patients were randomly assigned to amlodipine (10 mg once daily) and 128 to placebo. The primary endpoint was mortality from any cause. The secondary endpoint was a composite variable consisting of mortality from any cause or cardiovascular event. Analysis was by intention-to-treat. The trial was registered with ClinicalTrials.gov (number NCT00124969).

Results. The median age of patients was 61 years (25% percentile − 75% percentile, 47–69), and the median follow-up was 19 months (8–30). Fifteen (12%) of the 123 patients assigned to amlodipine and 22 (17%) of the 128 patients assigned to placebo had a primary endpoint [hazard ratio 0.65 (95% CI 0.34–1.23); $P = 0.19$]. Nineteen (15%) of the 123 haemodialysis patients assigned to amlodipine and 32 (25%) of the 128 haemodialysis patients assigned to placebo reached the secondary composite endpoint [hazard ratio 0.53 (95% CI 0.31–0.93); $P = 0.03$].

Conclusion. Amlodipine safely reduces systolic blood pressure and it may have a beneficial effect on cardiovascular outcomes in hypertensive haemodialysis patients.

Keywords: calcium channel blocker; cardiovascular risk; chronic kidney disease

The mortality rate in hypertensive patients with chronic kidney disease is substantially higher than in the general population [1–4]. Accelerated cardiovascular disease and increased macrovascular complications are the leading causes for increased morbidity and mortality in these patients. Several traditional risk factors including hypertension, diabetes mellitus and smoking can be observed in patients with chronic kidney disease. Furthermore, uraemia-related factors including oxidative stress and disturbances of calcium–phosphate metabolism have been associated with increased cardiovascular disease [5,6]. In the general population, calcium channel blockers are effective vasodilators and antihypertensive agents [7]. In prospective studies in hypertensive patients, an amlodipine-based regimen prevented more cardiovascular events than an atenolol-based regimen [8]. Furthermore, hypertensive patients receiving amlodipine had a significantly lower incidence of myocardial infarction compared to patients receiving valsartan [9]. These studies may give indirect evidence that the dihydropyridine calcium channel blocker could reduce macrovascular complications in hypertensive patients with chronic kidney disease. However, no prospective study has been performed to address that hypothesis in these high-risk patients. To date, a few retrospective cohort studies are available. Our previous retrospective study indicated that calcium channel blockers significantly reduced mortality in patients with chronic kidney disease stage 5 on haemodialysis treatment [10]. Furthermore, a retrospective analysis of data from United States Renal Data System Dialysis Morbidity and Mortality Wave II showed that the use of calcium channel blockers was associated with a 21% lower risk of total mortality in haemodialysis patients [11]. Our aim, therefore, was to ascertain whether the dihydropyridine calcium channel blocker amlodipine reduces mortality and cardiovascular events in hypertensive patients with chronic kidney disease stage 5.

Methods

Study protocol

The effects of amlodipine on mortality and cardiovascular events in hypertensive patients with chronic kidney disease stage 5 on haemodialysis treatment were investigated in an investigator-designed, prospective, randomized, double-blind, placebo-controlled, multicentre trial. The total trial duration of the trial was planned for 4 years. Recruitment

started on 01 October 2002 and ended on 30 March 2004. The trial was registered with ClinicalTrials.gov (number NCT00124969).

Patients

We prospectively studied 251 patients with chronic kidney disease stage 5 on haemodialysis treatment (159 males and 92 females) with a median age of 61 years (25% percentile − 75% percentile, 47–69). All of the patients were routinely dialyzed for 4–5 h three times weekly using biocompatible membranes with no dialyzer reuse. The dialysates used were bicarbonate based. All of the patients were ambulatory and free of acute intercurrent illness. Haemodialysis treatment was conducted in ambulatory dialysis centres according to established treatment guidelines. The participating centres are given in the Appendix. Patients were recruited from 47 centres, representing ∼2000 patients. The trial protocol was approved by all involved ethics committees and the trial was undertaken in accordance with the Declaration of Helsinki. Specifically, the ethical implications of the inclusion of a placebo group were taken into account and considered acceptable. All patients gave written, informed consent.

Inclusion criteria

The study included patients with chronic kidney disease stage 5 with presently existing arterial hypertension or with a history of arterial hypertension, i.e. resting blood pressure ≥140/90 mmHg or antihypertensive medication. Patients with chronic kidney disease stage 5 had been undergoing maintenance haemodialysis for a minimum of 3 months. The study included men and women. The study included patients 18 years and older.

Exclusion criteria

Exclusion criteria were persistent hypotension with systolic blood pressure of <90 mmHg, history of high-grade aortic stenosis, history of severe heart failure according to the New York Heart Association classification stages III and IV, acute myocardial infarction within the last 4 weeks, known allergy to amlodipine, and severe disorders of liver function, pregnancy or breast feeding. In patients who presently received any dihydropyridine calcium channel blockers, these drugs were withdrawn after giving informed consent and prior to randomization to the study medication. If these drugs could not be withdrawn according to the appraisal of the attending physician, these patients were excluded. Patients who did not give consent were excluded. Concomitant medication including angiotensin-converting enzyme inhibitors, beta (ß) blockers, lipid-lowering agents or erythropoietin was permitted as recommended by the attending physician.

Patients with chronic kidney disease stage 5 on haemodialysis treatment were randomly assigned either to receive amlodipine (10 mg once daily) or placebo. A computer-generated randomization list was prepared centrally guaranteeing that in study centres patients were assigned to one of both treatment groups. Eligible patients were assigned in a 1:1 ratio to receive amlodipine or placebo. The study medication was provided in externally indistinguishable tablets (appearance, form, colour, smell and taste). To ensure allocation concealment, sequentially numbered containers were used.

Baseline data collection

Patient history was raised using a standardized questionnaire and comprised personal histories, smoking habits, cause of kidney disease judged by clinical appraisal, months of haemodialysis treatment, pre-existing cardiovascular disease (i.e. history of myocardial infarction, need for coronary angioplasty or coronary bypass surgery, ischaemic stroke, peripheral vascular disease with the need for amputation or angioplasty), presence of diabetes mellitus and current medication including angiotensin-converting enzyme inhibitors, ß-blockers, lipid-lowering agents or erythropoietin. Blood pressure was always measured pre-dialysis after a rest period of 10 min of recumbency. Blood samples were drawn before the patients' regular haemodialysis session. Haemoglobin, serum creatinine, blood urea nitrogen, serum calcium, serum phosphate, parathyroid hormone, serum cholesterol and serum triglycerides were routinely analysed.

Outcomes

Patients were followed for 30 months. Data were continuously evaluated and recorded every 6 months. The primary endpoint was the time from randomization to mortality from any cause. The *post hoc* secondary endpoint was the time from randomization to the first event, which was a composite variable consisting of mortality from any cause, cardiac event including myocardial infarction, need for coronary angioplasty or coronary bypass surgery, ischaemic stroke, peripheral vascular disease with the need for amputation or angioplasty. Only one event per patient was included in the analysis of the secondary endpoint. Non-fatal myocardial infarction was defined according to the appraisal of the attending physician as the presence of at least two of the following criteria: chest pain of typical duration and intensity, increased cardiac enzyme concentrations (at least twice the upper limit of normal) and diagnostic electrocardiographical changes. Causes of death during the follow-up were classified as cardiovascular including sudden death, infection, cancer or other cause. Death occurring outside hospital for which no other cause was assigned was regarded as sudden death and was included in the definition of cardiovascular death. Deaths were classified by the treating physician independently of the endpoint analysis. Data on mortality were obtained for all patients. Patients who underwent kidney transplantation during the follow-up were censored on the day of transplantation. No patient was lost to the follow-up.

Adverse events and prespecified safety parameters were monitored throughout the study. A hypotensive episode was defined as an event with patients experiencing clinical symptoms associated with reduction of blood pressure during the haemodialysis treatment.

Statistical analysis

Our planned study sample size of 356 patients was based on the assumptions of a 40% mortality in the placebo group, a total trial duration of 4 years and a follow-up for each patient for 30 months. A time-to-event analysis was planned, and thus the study had 80% power to detect a 14% reduction in the hazard ratio with a type I error of 0.05. Because the total trial duration was planned for 4 years, and to ensure sufficient duration of exposure, i.e. until the last patient recruited had been followed up for 30 months, recruitment ended on 30 March 2004 although the enrolment rate was slower than planned and mortality rate was much lower than that expected from our earlier study [10].

Continuous data including age, months of haemodialysis treatment and biochemical data are reported as median (25% percentile − 75% percentile). The non-parametric Mann–Whitney test was used to detect differences in continuous variables between the treatment groups. Frequency counts were calculated for categorical data such as gender, specific medications and diagnostic classifications. Differences in these categorical variables between the treatment groups were analysed by Fisher's exact test. All time-to-event analyses were performed using the Mantel–Haenszel log-rank test. The hazard ratio and its 95% confidence interval are given. All analyses were based on the intention-to-treat principle. No interim analyses were done. The association of baseline characteristics including age, gender, smoking, presence of diabetes mellitus, medications (angiotensin-converting enzyme inhibitors, ß-blockers, erythropoietin and lipid-lowering agents), pre-existing cardiovascular disease, systolic and diastolic blood pressure and allocation to amlodipine to the primary endpoint (mortality) or the secondary combined endpoint was tested using the Cox proportional hazard model. In a stepwise forward Cox-regression analysis, variables with a P-value of 0.05 or less were retained. The effect of amlodipine on systolic blood pressure during the study period was compared to placebo using two-way ANOVA. Analyses were performed with GraphPad prism software (version 5.0, GraphPad Software, San Diego, CA, USA) or SPSS software (release 8.0.0, SPSS Inc., Chicago, IL, USA). All statistical tests were two sided. Two-sided P-values <0.05 were considered to indicate statistical significance.

Results

We investigated the effects of amlodipine on mortality and cardiovascular events in hypertensive patients with chronic kidney disease stage 5 on haemodialysis treatment in an investigator-designed, prospective, randomized, double-blind, placebo-controlled, multicentre trial. Figure 1 shows the flowchart of the study. The study was conducted using 251 patients with chronic kidney disease stage 5 on haemodialysis treatment [159 males, 92 females; median age, 61 years (25% percentile − 75% percentile, 47–69 years); systolic blood pressure 140 mmHg (130–160 mmHg) and diastolic blood pressure 80 mmHg (70–82 mmHg)] who had been undergoing maintenance

Table 1. Baseline characteristics of hypertensive patients with chronic kidney disease stage 5 on haemodialysis treatment

	Amlodipine group ($n = 123$)	Placebo group ($n = 128$)
Age (years)	60 (45–68)	62 (48–68)
Male n (%)	78 (63%)	81 (63%)
Body mass index (kg/m^2)	25.4 (22.6–28.9)	26.1 (23.4–28.7)
Renal disease n (%)		
Diabetic nephropathy	19 (15%)	26 (20%)
Nephrosclerosis	17 (14%)	26 (20%)
Chronic glomerulonephritis	39 (32%)	38 (30%)
Polycystic kidney disease and interstitial nephritis	30 (24%)	20 (16%)
Other/unknown	18 (15%)	18 (14%)
Months of haemodialysis	28 (12–48)	23 (13–43)
Systolic blood pressure (mmHg)	140 (128–160)	141 (130–160)
Diastolic blood pressure (mmHg)	80 (70–80)	80 (70–83)
Present smoker n (%)	24 (20%)	27 (21%)
Disease prevalence at baseline n (%)		
Diabetes mellitus	33 (27%)	40 (31%)
Cardiovascular disease	38 (31%)	44 (34%)
Haemoglobin (g/dL)	11.9 (11.0–12.7)	11.6 (10.7–12.4)
Serum creatinine (mg/dL)	10.0 (7.5–11.3)	9.0 (7.0–11.3)
Blood urea (mg/dL)	137 (113–174)	142 (110–166)
Total protein (g/dL)	6.7 (6.3–7.1)	6.8 (6.3–7.1)
Serum calcium (mmol/L)	2.3 (2.2–2.5)	2.3 (2.2–2.5)
Serum phosphate (mmol/L)	2.0 (1.7–2.6)	2.0 (1.6–2.4)
Parathyroid hormone (pg/mL)	188 (88–336)	216 (99–320)
Serum triglycerides (mg/dL)	175 (128–243)	158 (114–264)
Serum cholesterol (mg/dL)	171 (148–201)	176 (150–216)
Medications n (%)		
Angiotensin-converting enzyme inhibitors	79 (64%)	81 (63%)
ß-blockers	67 (54%)	79 (62%)
Erythropoietin	108 (88%)	108 (84%)
Lipid-lowering agents	53 (43%)	50 (39%)

Continuous data are shown as median (25% percentile − 75% percentile). Body mass index was calculated as the weight in kilograms divided by the square of the height in metres. There were no significant differences between the two groups.

haemodialysis for a minimum of 3 months three times weekly in ambulatory centres. The median duration of haemodialysis at the study entry was 27 months (12–46 months). The cause of chronic kidney disease stage 5 was diabetic nephropathy in 45 cases (18%), nephrosclerosis in 43 cases (17%), chronic glomerulonephritis in 77 cases (31%), polycystic kidney disease and interstitial nephritis in 50 cases (20%), and other/unknown in 36 cases (14%). Forty-one patients (13%) underwent kidney transplantation during the follow-up and were censored on the day of transplantation. One hundred twenty-three patients were randomly assigned to receive amlodipine (10 mg once daily) and 128 patients were randomly assigned to receive placebo. All patients commenced study medication and all received their intended treatment.

The baseline demographic, clinical and laboratory characteristics of the patients with chronic kidney disease stage 5 are described in Table 1. The two groups of patients were well matched with respect to baseline characteristics and concomitant therapy. There were no differences in baseline characteristics (age, gender, body mass index, renal disease,
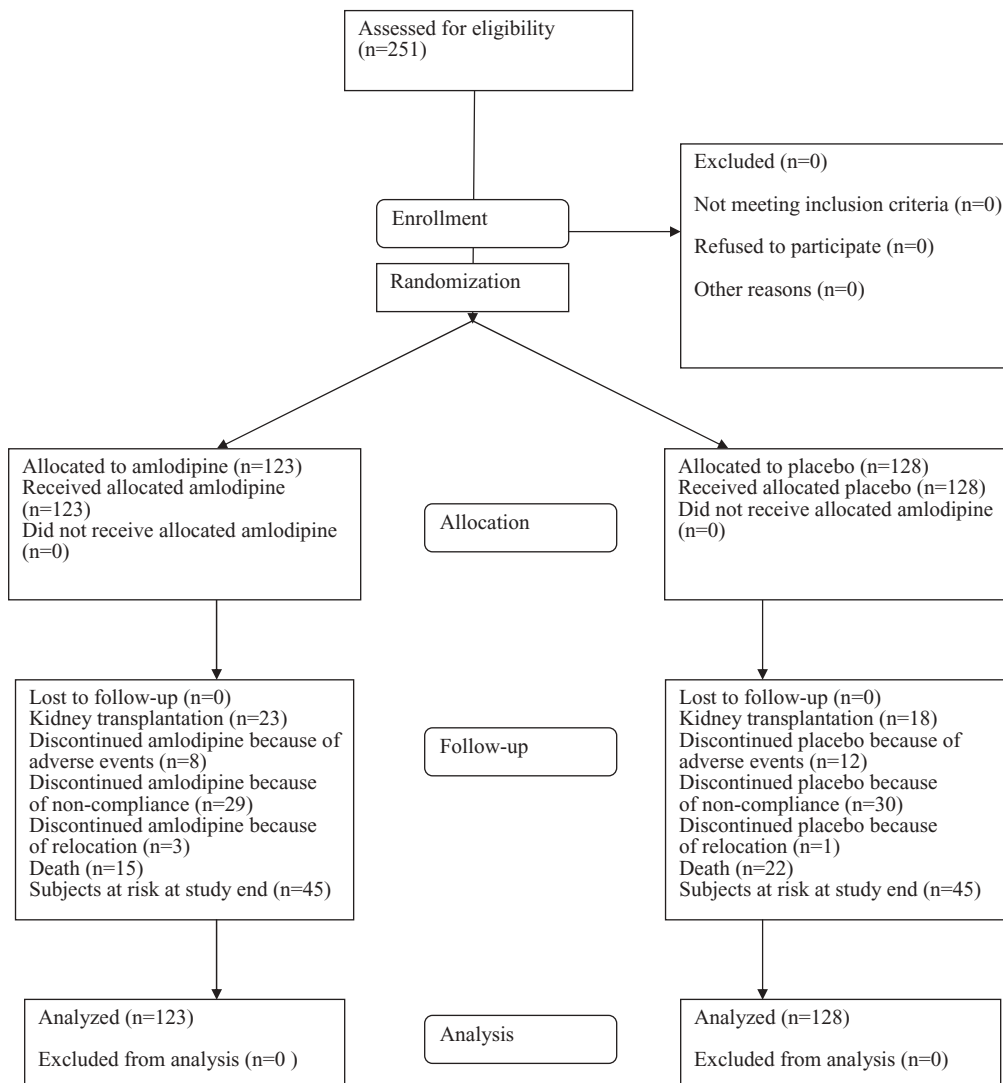
Fig. 1. The flowchart of the study trial.

months of haemodialysis, systolic and diastolic blood pressure, smoking status, biochemical data and medications) between the groups. In particular, haemoglobin concentrations, serum calcium, serum phosphate and parathyroid hormone were not significantly different between the two groups. As indicated by the body mass index, total protein and serum cholesterol, the nutritional status was not significantly different between the two groups. Use of angiotensin-converting enzyme inhibitors, ß-blockers, erythropoietin and lipid-lowering agents was not significantly different between the two groups. Furthermore, the prevalence of diabetes mellitus [amlodipine, 33 patients (27%); placebo, 40 patients (31%)] and of cardiovascular disease [amlodipine, 38 patients (31%); placebo, 44 patients (34%)] was similar in both groups.

Primary endpoint (mortality)

During the follow-up (median, 19 months; 8–30 months) the primary endpoint, i.e. mortality of all causes, was

reached in 37 out of 251 patients (15%). Causes of death were classified as cardiovascular including sudden death (26 patients; 70%), infection (7 patients; 19%) and cancer (4 patients; 11%). A total of 15 (12%) of the 123 haemodialysis patients assigned to amlodipine, and 22 (17%) of the 128 haemodialysis patients assigned to placebo had a primary endpoint. Figure 2 shows Kaplan–Meier estimates of the proportion of patients reaching the primary endpoint. Fewer patients in the amlodipine group than in the placebo group reached the primary endpoint, though this finding was not significant [hazard ratio 0.65 (95% CI 0.34–1.23); $P = 0.19$].

The association of baseline characteristics including age, gender, smoking, presence of diabetes mellitus, medications (angiotensin-converting enzyme inhibitors, ß-blockers, erythropoietin and lipid-lowering agents), pre-existing cardiovascular disease, systolic and diastolic blood pressure and allocation to amlodipine to the primary endpoint was tested using a multivariate analysis. Age [hazard ratio 1.06 (95% CI 1.02–1.08); $P < 0.01$], systolic blood
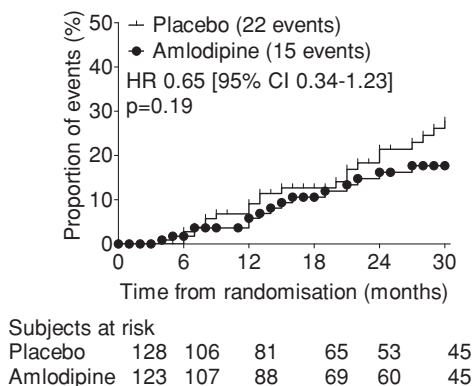
Fig. 2. Kaplan–Meier curve of time to the primary endpoint. The primary endpoint was mortality from any cause.

Fig. 3. Kaplan–Meier curve of time to the secondary endpoint. The secondary endpoint was a composite variable consisting of mortality from any cause, cardiac event including myocardial infarction, need for coronary angioplasty or coronary bypass surgery, ischaemic stroke, peripheral vascular disease with the need for amputation or angioplasty.

pressure [hazard ratio 1.02 (95% CI 1.00–1.04); $P = 0.02$], pre-existing cardiovascular disease [hazard ratio 2.38 (95% CI 1.10–5.11); $P = 0.03$] and smoking [hazard ratio 2.60 (95% CI 1.01–6.73); $P = 0.05$] were associated with the primary endpoint. The other baseline characteristics and allocation to amlodipine did not contribute significantly to the overall results.

Secondary composite endpoint

During the follow-up, the secondary endpoint, which was a composite variable consisting of mortality from any cause, cardiac event including myocardial infarction, need for coronary angioplasty or coronary bypass surgery, ischaemic stroke and peripheral vascular disease with the need for amputation or angioplasty, was reached in 51 out of 251 patients (20%). There were 33 deaths from any cause and 18 cardiovascular events. It should be noted that four patients who already had a cardiovascular event died during the subsequent follow-up, but only the time to the first event was considered for the secondary composite endpoint.

Cardiovascular events were classified as cardiac event (11 patients; 61%), stroke (2 patients; 11%) and amputation (5 patients; 28%).

A total of 19 (15%) of the 123 haemodialysis patients assigned to amlodipine and 32 (25%) of the 128 haemodialysis patients assigned to placebo reached the secondary endpoint. Figure 3 shows Kaplan–Meier estimates of the proportion of patients reaching the secondary endpoint. Fewer patients in the amlodipine group than in the placebo group reached the secondary endpoint [hazard ratio 0.53 (95% CI 0.31–0.93); $P = 0.03$]. The difference was significant. The patients in the amlodipine group had a risk of reaching the secondary endpoint that was 47% lower compared to the placebo group.

The association of baseline characteristics including age, gender, smoking, presence of diabetes mellitus, medications (angiotensin-converting enzyme inhibitors, ß-blockers, erythropoietin and lipid-lowering agents), pre-existing cardiovascular disease, systolic and diastolic blood pressure and allocation to amlodipine to the secondary endpoint was tested using a multivariate analysis. Amlodipine was associated with the secondary composite endpoint with a hazard ratio of 0.55 [(95% CI 0.31–0.97); $P = 0.04$] even
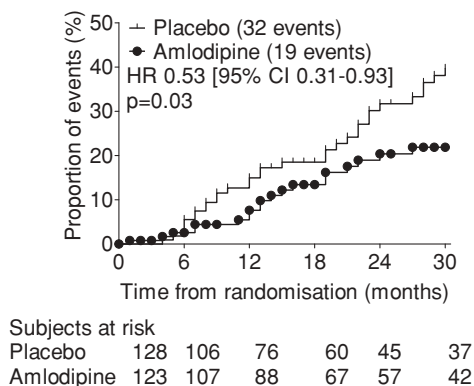
after adjustment for the other baseline characteristics. Pre-existing cardiovascular disease predicted the occurrence of the secondary composite endpoint [hazard ratio 3.34 (95% CI 1.91–5.86); $P < 0.01$]. The other baseline characteristics did not contribute significantly to the overall results.

We also analysed subclasses of patients to evaluate the underlying mechanisms of the observed effects. In patients who had received any dihydropyridine calcium channel blockers, these drugs were withdrawn after giving informed consent and prior to randomization to the study medication. Ninety-one patients had been treated with calcium channel blockers before the start of the study. After randomization, 42 patients received amlodipine, whereas 49 patients received placebo. Five (12%) out of 42 patients receiving amlodipine, but 15 (31%) out of 49 patients receiving placebo had a cardiovascular event [relative risk 0.39 (95% CI 0.15–0.98); $P = 0.04$]. One hundred and sixty hypertensive patients on haemodialysis had not been treated with calcium channel blockers before the start of the study. After randomization, 80 patients received amlodipine, whereas 80 patients received placebo. Thirteen (16%) out of 80 patients receiving amlodipine, but 18 (23%) out of 80 patients receiving placebo had a cardiovascular event [relative risk 0.72 (95% CI 0.38–1.37); $P = 0.42$].

The course of systolic and diastolic blood pressure during the study is shown in Figure 4. Two-way ANOVA showed a significant reduction of systolic blood pressure by amlodipine during the study period ($P < 0.01$) from 140 mmHg (128–160 mmHg) to 130 mmHg (120–147 mmHg), whereas systolic blood pressure was unchanged in the placebo group (141 mmHg, 130–160 mmHg; and 140 mmHg, 130–150 mmHg). Diastolic blood pressure did not change during the study period in either group ($P > 0.05$).

Hypotensive episodes, i.e. patients experiencing clinical symptoms associated with the reduction of blood pressure during the haemodialysis treatment, were not significantly different in the amlodipine group, compared to placebo. A total of 9 (7%) of the 123 haemodialysis patients assigned to amlodipine and 16 (13%) of the 128 haemodialysis patients
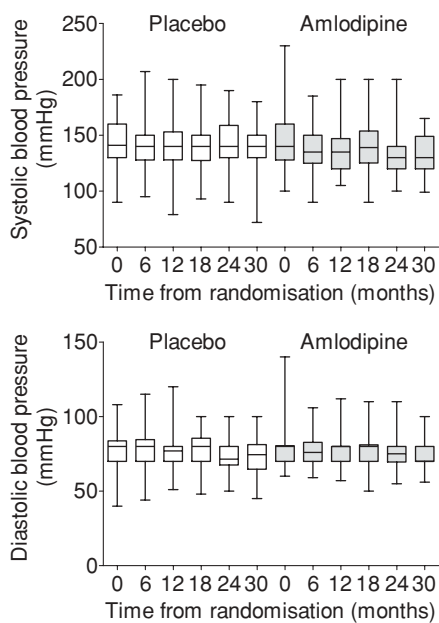
Fig. 4. Systolic (upper panel) and diastolic (lower panel) blood pressure during the study in the placebo group and in the amlodipine group. Boxes show 25% percentile, median and 75% percentile; whiskers show minimum and maximum. Two-way ANOVA showed a significant reduction of systolic blood pressure by amlodipine during the study period ($P < 0.01$), whereas systolic blood pressure was unchanged in the placebo group. Diastolic blood pressure did not change during the study period in either group ($P > 0.05$).

assigned to placebo had a hypotensive episode [relative risk 0.58 (95% CI 0.27–1.28); $P = 0.21$].

Discussion

Our findings show that amlodipine non-significantly reduces the primary endpoint, i.e. all-cause mortality, by 35% in hypertensive patients with chronic kidney disease stage 5. Although it did not reach statistical significance, it may, however, be clinically relevant considering the excess mortality in these high-risk patients. The primary endpoint had been designed assuming a mortality of 40% in 30 months whereas in the present study, mortality was 15%. Furthermore, many more patients than expected underwent kidney transplantation during the course of the study.

However, this prospective, randomized study for the first time demonstrated that amlodipine (10 mg once daily) reduces the secondary composite endpoint that included mortality from any cause, cardiac event including myocardial infarction, need for coronary angioplasty or coronary bypass surgery, ischaemic stroke and peripheral vascular disease with the need for amputation or angioplasty in these patients with a high risk of macrovascular events. The use of amlodipine was associated with a significant reduction of the secondary composite endpoint by 47% in hypertensive patients with chronic kidney disease stage 5.

The *post hoc* definition of the secondary composite endpoint considered the high risk of macrovascular events in

these patients with chronic kidney disease stage 5 and respective established outcome definitions reported in previous studies in these patients [12–14]. This secondary composite endpoint was significantly reduced by administration of amlodipine. The favourable effect of the calcium channel blocker amlodipine should be compared to the reported effects of other treatment modalities in patents with chronic kidney disease stage 5. A recent study indicated that lipid-lowering drugs had no statistically significant effect on the composite endpoint of cardiovascular death, non-fatal myocardial infarction and stroke in diabetic patients with chronic kidney disease stage 5 [12].

According to the study protocol, patients were treated according to the established treatment guidelines and >50% of the patients received angiotensin-converting enzyme inhibitors or ß-blockers. Although the use of additional antihypertensive drugs was permitted in the study protocol, the cause of different systolic blood pressure values during the course of the study remains unclear. It is noteworthy that hypotensive episodes were observed more frequently in the placebo group compared to the amlodipine group (13% versus 7%), although that difference did not reach a statistical significance. Patients in the amlodipine group developed lower systolic blood pressure during the study period. The beneficial effects of amlodipine to prevent the secondary composite endpoint might be attributed to its antihypertensive effects. That finding is in accordance with results from the VALUE trial showing a beneficial effect of amlodipine versus valsartan due to low blood pressure [13].

It is important to note that systolic and diastolic blood pressure was not significantly different between the two groups at the start of the study. On the other hand, the analysis of subclasses of patients showed a slightly significant beneficial effect in the amlodipine group in patients who had been treated with calcium channel blockers earlier but not in patients who had not been treated with calcium channel blockers. These findings may point to a protective class effect of calcium channel blockers in hypertensive patients on haemodialysis. However, further studies are needed to clarify that point. Furthermore, in the literature there are somewhat discrepant results as to whether the elevated systolic blood pressure contributes to mortality in patients with chronic kidney disease stage 5. In one study including 195 incident haemodialysis patients, those patients who died within 3 years after the introduction of haemodialysis had higher age and higher systolic blood pressure compared to survivors [14]. Another study in 432 patients with chronic kidney disease stage 5 showed the importance of co-morbidity. Each 10 mmHg rise in mean arterial blood pressure was independently associated with the presence of left ventricular hypertrophy. Consecutive cardiac failure was followed by reduced blood pressure and the degree of hypotension was a predictor of mortality [15]. In a cohort of 40 933 haemodialysis patients in the USA, the lowest mortality was associated with predialysis systolic pressure of 160–189 mmHg, whereas normal to low predialysis pressure values were associated with significantly increased mortality [16]. Furthermore, in a cohort of 69 590 prevalent haemodialysis patients, the 1-year hazard ratio for death was significantly higher in patients with

systolic blood pressure <140 mmHg compared to the reference group with systolic blood pressure of 160–180 mmHg [17,18]. Furthermore, the effect of amlodipine might also be attributed to other mechanisms, including reduced asymmetric dimethylarginine [19].

Limitations of the study

Some limitations of our randomized, double-blind, prospective study were that the enrolment rate was slower than planned, diabetic nephropathy was lower than expected, the transplantation rate was high and the mortality rate was lower than expected. For each patient, a follow-up period of 30 months was provided. Each patient was followed up until the endpoint (mortality) was reached or the patient terminated the study or the patient was transplanted. This is in accordance to the initial study plan. However, the final analysis showed that the actual median follow-up time was 19 months. All these points may have reduced the power of the study to detect a reduction of mortality in the amlodipine group. These factors may explain the absence of a significant effect of amlodipine on the primary endpoint. Another limitation of the study may be that the median duration of haemodialysis before enrolment was more than 23 months; hence, the results of the study may not be representative for incident haemodialysis patients. These points may also indicate that the generalizability of the study findings may be limited.

In summary, the present study shows that amlodipine safely reduces systolic blood pressure and that it may have a beneficial effect on cardiovascular outcomes in hypertensive haemodialysis patients. Further studies are needed to support these findings.

Appendix

Contributors

Dr Tepel and Dr Hopfenmueller had full access to all the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit for publication. All authors and the study sponsor agreed to submit the paper for publication. Study concept and design: Tepel, Hopfenmueller. Acquisition of data: Tepel, Scholze and Maier. Analysis and interpretation of data: Tepel, Hopfenmueller, Scholze, Maier and Zidek. Drafting of the manuscript: Tepel, Hopfenmueller and Zidek. Critical revision of the manuscript for important intellectual content: Tepel, Hopfenmueller, Scholze, Maier and Zidek. Statistical analysis: Tepel and Hopfenmueller. Obtained funding: Tepel. Administrative, technical or material support: Tepel, Scholze and Maier. Study supervision: Tepel and Zidek.

Participating centres

Dr Vollgraf, Dr Hahn, Dortmund; Dr Schumann, Dr Reinhardt, Herne; Dr Bednarz, Dr Clasen, Münster; Dr Hoffmann, Dr Witta, Hamm; Dr Kriegel, Dr Kresse, Lutherstadt Eisleben; Dr Kallerhoff, Dr Selke, Bocholt; Dr Fendt, Berlin; Dr Lange, Dr Oppermann, Perleberg; Dr Braun, Berlin; Dr Bartke, Dr Eger, Berlin; Dr Cleef, Dr Brauner, Berlin; Dr Nielebock, Dr Gosch, Magdeburg; Dr Striebing, Dessau; Dr Kron, Dr Leimbach, Berlin; Dr Poley, Dr Francke, Seehausen Altmark; Dr Lüders, Dr Schrader, Cloppenburg; Dr Bachmann, Arnsberg; Dr Michling, Recklinghausen; Dr Brückner, Dr Willeke, Dortmund; Dr Riedasch, Dr Schreiber, Coesfeld; Dr Baus, Dr Schaper, Frankfurt/Oder; Dr Markus, Frankfurt/Oder; Dr Wiedemeyer, Dortmund; Dr Braasch, Eberswalde; Th. Lindner, Dipl.Med. Rebhan, Hennigsdorf; Dr Enke, Dr Müller, Zeitz; Dr Rösch, Dr Theunert, Dessau; Dr Meyer, Heidenau; Dr Heinrich, Dr Adler, Dipl.Med. Schindler, Freiberg; Dr Hans, Dr Neumann, Dresden; Dr Berger, Dr Tendis, Borna; Dr Schlöcker, Wolfenbüttel; Dr Meistring, Görlitz; Dr Brockmann, Bad Bevensen; Dr Haaf, Wismar; Dr Dressler, Dr Rhode, Hofgeismar; Dr Lammers, Dr Meyer, Oldenburg; Dr Florschütz, Schmalkalden; Dr Bunia, Dr Ernst, Iserlohn; Dr Schulz, Hassfurt; Dr Rob, Dr Hennings, Lübeck; Dr Vögele-Dirks, Dr Riedl, Bayreuth; Dr Hägel, Dr Wichmann, Bayreuth; Dr Blaser, Dr Grunewald, Lohr; Dr Jensen, Dr Piper, Wiesbaden; Dr Lufft, Dr Klause, Rendsburg; Dr Stefovic-Fuchs, Dr Braun, Dingolfing; all from Germany.

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