Impact of long-acting calcium channel blockers on the prognosis of patients with coronary artery disease with and without chronic kidney disease: A comparison of three drugs

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Impact of Long-acting Calcium Channel Blockers on the Prognosis of Patients with Coronary Artery Disease With and Without Chronic Kidney Disease: a Comparison of Three Drugs

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Calcium channel blockers (CCBs) can prevent cardiovascular events in patients with coronary artery disease (CAD). This study looked retrospectively at the prognosis of CAD in hypertensive patients with CAD who had undergone a coronary angiograph, had been given a CCB (benidipine [*n* = 66], amlodipine [*n* = 45], or long-acting nifedipine [*n* = 31]) on hospital discharge and were then followed up for a mean ± SD of 5.2 ± 2.9 years. Systolic/diastolic blood pressure for all 142 patients decreased significantly from a mean ± SD of 137 ± 20/74 ± 15 mmHg to 129 ± 20/71 ± 12 mmHg. Major adverse cardiovascular events (MACE) occurred in 15 patients. Chronic kidney disease (CKD) was a significant risk factor for MACE (hazard ratio 2.35, 95% confidence intervals 1.45, 3.80). Benidipine was superior to nifedipine in preventing MACE in patients both with and without CKD. In conclusion, benidipine and amlodipine reduced the frequency of MACE in hypertensive patients with CAD, particularly in those with complicating CKD.

KEY WORDS: Coronary artery disease; Hypertension; Cardiovascular disease; Chronic Kidney disease; Calcium channel blocker; Benidipine; Amlodipine; Nifedipine; Prognosis

Introduction

Calcium channel blockers (CCBs) are widely used in the treatment of angina pectoris and hypertension, primarily based on their actions as coronary artery vasodilators. Long-acting CCBs have also been shown to prevent cardiovascular events in hypertensive patients.[1,2] The CCBs are known to be effective in reducing cardiovascular mortality and morbidity in patients with angina pectoris,[3,4] especially those with underlying hypertension.[5,6]

Ischaemic heart disease and myocardial infarction in the Japanese population are characterized by their frequent association with coronary vasospasm.[7,8] The CCBs have

been shown to be highly effective in patients with vasospastic angina,[9] and studies have demonstrated the effects of different CCBs on the risk of developing cardiovascular events in patients with vasospastic angina.[10 – 12] Only limited information is available on whether the effects of CCBs in preventing the development of cardiovascular events might vary with the drug class in patients with coronary artery disease (CAD) associated with organic stenosis.

In the present retrospective, observational study, patients diagnosed with both hypertension and CAD who were prescribed CCBs at the time of discharge from hospital were identified from a coronary angiography database. The aim of the study was to identify the risk factors for developing major adverse cardiovascular events (MACE) and to evaluate any differences in the CCBs in preventing MACE.

Patients and methods

PATIENTS

Patients diagnosed with both hypertension and CAD who were prescribed CCBs on the day of discharge from hospital were retrospectively identified from a database of consecutive patients who underwent coronary angiography between 1 January 1995 and 30 September 2006 at the Department of Cardiovascular Medicine, Toyama Red Cross Hospital, Toyama, Japan. All patients fulfilling these criteria and for whom follow-up data were available were included in the analysis. A follow-up inquiry about the patients' present status, including survival and complications, as of 1 January 2008 was carried out by mail and telephone for all included patients. The study was conducted with the approval of the Institutional Review Board of Toyama Red Cross Hospital. All participants (or their representatives) provided written and verbal informed consent to be included in the study.

In this study, CAD was defined as the occurrence of ≥ 75% stenosis in at least one principal coronary artery, in accordance with the classification of the American Heart Association,[13] and hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and/or a diastolic blood pressure of ≥ 90 mmHg, in accordance with the Japanese Society of Hypertension Guidelines for the Management of Hypertension.[14] The doses of CCBs were (mean ± SD): benidipine 6.7 ± 1.9 mg/day, amlodipine 5.1 ± 1.2 mg/day, and nifedipine 40.6 ± 12.9 mg/day.

DATA COLLECTION

The database and medical records were reviewed for patient characteristics at the time of coronary angiography (baseline) and for the angiographic findings. Details of the treatment employed, such as percutaneous coronary intervention, coronary artery bypass grafting, and medications taken were also collated from the medical records.

An estimated glomerular filtration rate, as estimated from the serum creatinine concentration using the Modification of Diet in Renal Disease (MDRD) study equation, of < 60 min/ml per 1.73 m^2 for ≥ 3 months prior to baseline was considered to be indicative of chronic kidney disease (CKD).[15] The pressure–rate product (PRP) was calculated by multiplying the systolic blood pressure and the heart rate. The systolic, diastolic and mean blood pressures, heart rate, PRP and frequency of angina attacks as determined at the last visit or at the onset of MACE were compared with the values at baseline.

The location and extent of coronary artery stenotic lesions in the coronary angiograph obtained at baseline were expressed according to the American Heart Association classification.[13] The presence of stenosis in the principal coronary arteries,

such as in the right coronary artery, left circumflex artery and left anterior descending artery, the number of vessels showing stenotic lesions, and the presence of significant multivessel stenosis were also determined.

STUDY ASSESSMENTS

The primary outcome in this study was the frequency of occurrence of MACE: cardiac death, fatal or non-fatal myocardial infarction, or unstable angina pectoris requiring hospitalization. Patient characteristics, coronary angiography findings and treatment regimens at baseline were assessed to identify risk factors for MACE. Changes in the systolic, diastolic and mean blood pressures, heart rate and PRP from baseline to the last visit were evaluated and their potential relationship with the incidence of MACE determined.

Other outcomes included the incidence of revascularization, incidence of fatal or non-fatal stroke, and progression to end-stage renal disease (ESRD). In this study, ESRD was defined as a doubling of the baseline serum creatinine concentration or a serum creatinine concentration of ≥ 1.5 mg/dl. Information on the nature and date of onset of MACE occurring during the follow-up period up to 1 January 2008 were also collected. The influence of the patient characteristics and the prophylactic effect of each CCB against the development of MACE were also assessed.

STATISTICAL ANALYSIS

Data were expressed as mean ± SD. Cox regression analysis was used to identify the factors determining the primary outcome, namely, the frequency of development of MACE. Kaplan–Meier survival curves of the risk factors identified in relation to the CCBs used were generated to estimate the time to MACE. Changes in the systolic, diastolic and mean blood pressures, heart rate and PRP from the baseline to the last visit were analysed using the paired *t*-test. Differences in the frequency of angina attacks were evaluated by Wilcoxon's *U*-test and Mann–Whitney's *U*-test. Kaplan–Meier curves were generated to compare the time-to-event between the treatments and the data were analysed by the log-rank test. Statistical analyses were carried out using the SPSS® statistical package, version 11.01J (SPSS Inc., Chicago, IL, USA) for Windows®. The two-sided level of significance was set at 5% ($P < 0.05$).

Results

PATIENTS

From the database, 164 patients diagnosed with both hypertension and CAD and who were prescribed CCBs on the day of hospital discharge were identified and, of these, 142 patients had follow-up data available and were included in the analysis. Patient characteristics and angiographic findings at the time of coronary angiography (baseline) are shown in Table 1. Of the 142 patients included in the analysis, 66 received benidipine, 45 received amlodipine and 31 received nifedipine. There were no significant differences among the three treatment groups in baseline characteristics, except for concurrent hyperlipidaemia. Percutaneous coronary intervention was carried out in 105 (74%) of the 142 patients.

Details of the treatment employed and medications prescribed at discharge are shown in Table 2. The use of different interventional techniques, including balloon angioplasty and stenting with a bare metal stent or a drug-eluting stent, was similar among the three treatment groups. Neither the subject characteristics nor the CCBs used were different before or after the introduction

TABLE 1:
Characteristics and angiographic findings for the patients with coronary artery disease and hypertension at the time of coronary angiography (baseline), stratified according to calcium channel blocker treatment after hospital discharge

Characteristic	Overall (n = 142)	Benidipine (n = 66)	Amlodipine (n = 45)	Nifedipine (n = 31)	Statistical significance[a]
Sex, *n* (%)					
Male	98 (69)	44 (67)	31 (69)	23 (74)	NS
Female	44 (31)	22 (33)	14 (31)	8 (26)	
Age					
Mean ± SD, years	66.6 ± 9.3	65.7 ± 9.5	65.7 ± 9.3	69.9 ± 8.2	NS
≥ 65 years, *n* (%)	88 (62)	40 (61)	26 (58)	22 (71)	NS
BMI					
Mean ± SD, kg/m^2	24.4 ± 3.7 2	4.2 ± 4.4	24.5 ± 2.8	24.6 ± 3.2	NS
≥ 25 kg/m^2, *n* (%)	50 (35)	20 (30)	19 (42)	11 (35)	NS
Smoking, *n* (%)					
Never	62 (44)	30 (45)	21 (47)	11 (35)	NS
Former	43 (30)	18 (27)	14 (31)	11 (35)	
Current	34 (24)	15 (23)	10 (22)	9 (29)	
Family history of IHD, *n* (%)	15 (11)	11 (17)	3 (7)	1 (3)	NS
Previous myocardial infarction, *n* (%)	41 (29)	20 (30)	14 (31)	7 (23)	NS
Hyperlipidaemia, *n* (%)	69 (49)	38 (58)	22 (49)	9 (29)	P = 0.032
Diabetes mellitus, *n* (%)	49 (35)	18 (27)	17 (38)	14 (45)	NS
CKD, *n* (%)	52 (37)	27 (41)	16 (36)	9 (29)	NS
eGFR, *n* (%)	64.9 ± 22.8	66.0 ± 21.2	65.5 ± 23.0	61.8 ± 26.2	NS
Previous stroke, *n* (%)	19 (13)	10 (15)	4 (9)	5 (16)	NS
LVEF					
Mean ± SD, %	61.3 ± 12.2	58.8 ± 12.7	64.3 ± 11.4	62.5 ± 11.4	NS
< 50%, *n* (%)	17 (12)	11 (17)	4 (9)	2 (6)	NS
Vessel branches showing significant stenosis, *n* (%)					
RCA	76 (54)	35 (53)	25 (56)	16 (52)	NS
LCA	91 (64)	45 (68)	29 (64)	17 (55)	NS
LCX	57 (40)	29 (44)	15 (33)	13 (42)	NS

TABLE 1 (continued):
Characteristics and angiographic findings for the patients with coronary artery disease and hypertension at the time of coronary angiography (baseline), stratified according to calcium channel blocker treatment after hospital discharge

Characteristic	Overall (n = 142)	Benidipine (n = 66)	Amlodipine (n = 45)	Nifedipine (n = 31)	Statistical significance[a]
No. of vessels showing significant stenosis, n (%)					
1	77 (54)	31 (47)	28 (62)	18 (58)	NS
2	48 (34)	27 (41)	10 (22)	11 (35)	
3	17 (12)	8 (12)	7 (16)	2 (6)	
Significant multivessel stenosis, n (%)	65 (46)	35 (53)	17 (38)	13 (42)	NS

[a]Comparison between the three groups used the χ^2-test and Mann–Whitney U-test.
Calcium channel blocker dose (mean ± SD): benidipine 6.7 ± 1.9 mg/day; amlodipine, 5.1 ± 1.2 mg/day; long-acting nifedipine, 40.6 ± 12.9 mg/day.
BMI, body mass index; IHD, ischaemic heart disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; RCA, right coronary artery; LCA, left anterior descending artery; LCX, left circumflex artery; NS, not statistically significant ($P > 0.05$).

of drug-eluting stents. At baseline, angiotensin II receptor blockers (ARBs) were used most frequently in the nifedipine treatment group ($P < 0.001$). The CCB dose at baseline was (mean ± SD) 6.7 ± 1.9 mg/day for benidipine, 5.1 ± 1.2 mg/day for amlodipine and 40.6 ± 12.9 mg/day for nifedipine. The proportion of patients who continued to take a CCB until their last visit was 44/66 (66.7%) in the benidipine group, 28/45 (62.2%) in the amlodipine group, and 21/31 (67.7%) in the nifedipine group.

STUDY OUTCOMES

The primary outcome, MACE, occurred in 15 patients, consisting of cardiac death in six cases, non-fatal myocardial infarction in four cases and unstable angina in five cases. Three of the cardiac deaths were attributable to myocardial infarction. Analysis of the risk factors for MACE amongst all the patients studied is shown in Table 3. The hazard ratio for MACE was 2.35 (95% confidence intervals [CI] 1.45, 3.80; $P = 0.001$) for those with concurrent CKD and 0.94 (95% CI 0.89, 1.00; $P = 0.038$) for change in heart rate from baseline. The incidence of MACE was significantly higher in subjects with CKD than in those without CKD (Fig. 1). The effects of the three CCBs in preventing the occurrence of MACE were compared in the patients with CKD (n = 52) (Fig. 2). Benidipine and amlodipine were significantly more effective than nifedipine ($P = 0.004$ and $P < 0.001$, respectively) in preventing MACE in this population, just as in the entire population.

Benidipine was associated with a low hazard ratio of 0.28 (95% CI 0.08, 1.00; $P = 0.049$) for MACE, in contrast to a high hazard ratio of 5.26 for nifedipine (95% CI 1.83, 15.15; $P = 0.002$) (Table 4). For all-cause mortality, the hazard ratio was high in the nifedipine group (3.83; $P = 0.004$).

TABLE 2:
Treatments given to the patients with coronary artery disease and hypertension at the time of coronary angiography and the medications prescribed at discharge, stratified according to calcium channel blocker treatment after hospital discharge

Treatment/medication	Overall (n = 142)	Benidipine (n = 66)	Amlodipine (n = 45)	Nifedipine (n = 31)	Statistical significance[a]
PCI, *n* (%)	105 (74)	51 (77)	31 (69)	23 (74)	NS
Balloon angioplasty, *n* (%)	36 (34)	16 (31)	14 (45)	6 (26)	NS
Bare metal stent, *n* (%)	55 (52)	30 (59)	12 (39)	13 (57)	NS
Drug-eluting stent, *n* (%)	20 (19)	11 (22)	5 (16)	4 (13)	NS
Other, *n* (%)	3 (3)	2 (4)	1 (3)	0 (0)	NS
CABG, *n* (%)	17 (12)	7 (11)	6 (13)	4 (13)	NS
Medication prescribed at discharge, *n* (%)					
Aspirin	142 (100)	66 (100)	45 (100)	31 (100)	–
Statins	51 (36)	27 (41)	14 (31)	10 (32)	NS
ARBs	31 (22)	17 (26)	2 (4)	12 (39)	$P < 0.001$
ACE inhibitors	13 (9)	2 (3)	7 (16)	4 (13)	NS
β-Blockers	16 (11)	9 (14)	4 (9)	3 (10)	NS
Nitrates	97 (68)	41 (62)	33 (73)	23 (74)	NS

[a]Comparison between the three groups used the χ^2-test and Mann–Whitney *U*-test.
Calcium channel blocker dose: (mean ± SD) benidipine 6.7 ± 1.9 mg/day; amlodipine, 5.1 ± 1.2 mg/day; long-acting nifedipine, 40.6 ± 12.9 mg/day.
PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ARBs, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme; NS, not statistically significant ($P > 0.05$).

TABLE 3:
Analysis to identify the risk factors for major adverse cardiovascular events (MACE) following coronary angiography and calcium channel blocker treatment after hospital discharge in patients with coronary artery disease and hypertension (n = 142)

Characteristic	Hazard ratio	Hazard ratio 95% CI		Statistical significance[a]
		Lower	Upper	
Age, ≥ 65 years	1.08	0.38	3.04	NS
Sex, female	1.27	0.43	3.72	NS
Body mass index, ≥ 25 kg/m^2	0.59	0.18	1.89	NS
Hyperlipidemia	1.76	0.62	4.96	NS
Diabetes mellitus	1.58	0.56	4.45	NS
Chronic kidney disease	2.35	1.45	3.80	P = 0.001
Previous myocardial infarction	1.32	0.47	3.69	NS
Previous stroke	1.01	0.23	4.48	NS
LVEF, < 50%	1.39	0.36	5.39	NS
Multivessel stenosis	1.44	0.52	3.97	NS
No. of vessels showing significant stenosis	1.45	0.76	2.76	NS
Percutaneous coronary intervention	0.68	0.24	1.92	NS
Balloon angioplasty	0.43	0.12	1.56	NS
Bare metal stent	1.01	0.34	3.01	NS
Drug-eluting stent	2.51	0.26	24.62	NS
Coronary artery bypass grafting	1.46	0.41	5.17	NS
Statins	1.64	0.58	4.65	NS
ARBs	1.52	0.32	7.32	NS
ACE inhibitors	2.10	0.59	7.48	NS
β-Blockers	0.92	0.21	4.08	NS
Systolic blood pressure at baseline	0.99	0.96	1.02	NS
Diastolic blood pressure at baseline	0.97	0.93	1.01	NS
Mean blood pressure at baseline	0.97	0.94	1.01	NS
Heart rate at baseline	0.98	0.90	1.06	NS
Pressure–rate product at baseline	1.00	1.00	1.00	NS
Change in systolic blood pressure	1.00	0.98	1.02	NS
Change in diastolic blood pressure	0.98	0.96	1.01	NS
Change in mean blood pressure	0.99	0.97	1.02	NS
Change in heart rate	0.94	0.89	1.00	P = 0.038
Change in pressure–rate product	1.00	1.00	1.00	NS

[a]The identification of risk factors for MACE used univariate Cox regression analysis.
Coronary angiography carried out between January 1995 and September 2006, and followed up in January 2008.
Calcium channel blocker dose: (mean ± SD): benidipine 6.7 ± 1.9 mg/day; amlodipine, 5.1 ± 1.2 mg/day; long-acting nifedipine, 40.6 ± 12.9 mg/day.
LVEF, left ventricular ejection fraction; ARBs, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme; NS, not statistically significant (P > 0.05); CI, confidence interval.

Interestingly, benidipine decreased the hazard ratio for progression to ESRD to 0.38, although this did not reach statistical significance in the population studied.

Kaplan–Meier curves were generated to compare the time-to-event between the treatments. There were no significant differences in the duration of follow-up (mean ± SD 5.2 ± 2.9 years; median 5.3 years) among the three groups. Benidipine

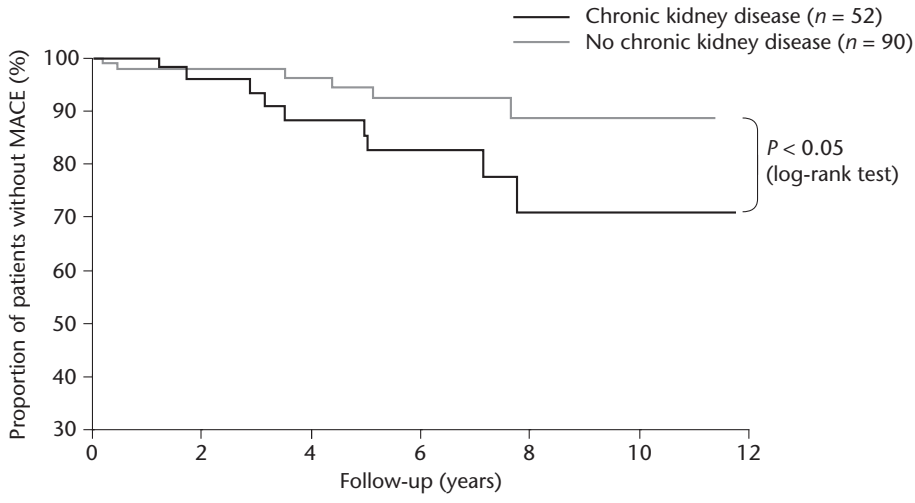

FIGURE 1: The effect of chronic kidney disease on the time to a major adverse cardiovascular event (MACE) in patients who also had coronary artery disease and hypertension and underwent coronary angiography and discharge from hospital on a calcium channel blocker (mean ± SD dose: benidipine 6.7 ± 1.9 mg/day, amlodipine 5.1 ± 1.2 mg/day or long-acting nifedipine 40.6 ± 12.9 mg/day)

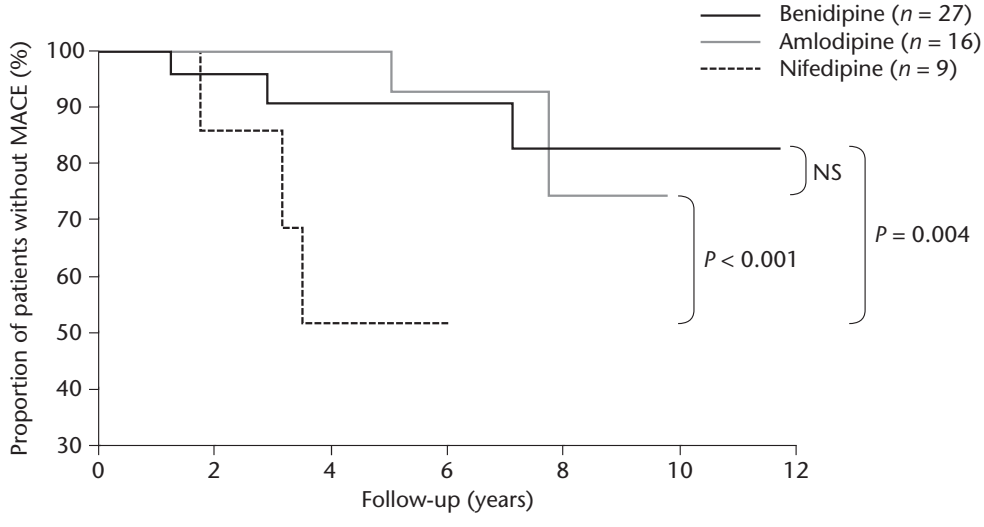

FIGURE 2: Effect of the different calcium channel blockers on the time to occurrence of a major adverse cardiovascular event (MACE) in patients with chronic kidney disease (n = 52) who also had coronary artery disease and hypertension and underwent coronary angiography (mean ± SD dose: benidipine 6.7 ± 1.9 mg/day, amlodipine 5.1 ± 1.2 mg/day or long-acting nifedipine 40.6 ± 12.9 mg/day) (NS, not statistically significant [$P > 0.05$])

and amlodipine were both significantly superior to nifedipine ($P < 0.001$ and $P = 0.018$ respectively) in preventing the development of MACE (Fig. 3A). The

TABLE 4:
Prophylactic effect of calcium channel blockers on the occurrence of major adverse cardiovascular events (MACE), cardiac death, all-cause mortality, stroke and end-stage renal disease (ESRD) following coronary angiography in patients with coronary artery disease and hypertension

Event	No. (%) of events	Hazard ratio	Hazard ratio 95% CI		Statistical significance[a]
			Lower	Upper	
MACE					
Benidipine (*n* = 66)	3 (4.5)	0.28	0.08	1.00	*P* = 0.049
Amlodipine (*n* = 45)	5 (11.1)	0.82	0.28	2.40	NS
Nifedipine (*n* = 31)	7 (22.6)	5.26	1.83	15.15	*P* = 0.002
Cardiac death					
Benidipine (*n* = 66)	2 (3.0)	0.28	0.06	1.41	NS
Amlodipine (*n* = 45)	1 (2.2)	0.22	0.03	1.78	NS
Nifedipine (*n* = 31)	6 (19.4)	11.24	2.75	45.92	*P* < 0.001
All-cause mortality					
Benidipine (*n* = 66)	5 (7.6)	0.36	0.13	1.01	NS
Amlodipine (*n* = 45)	7 (15.6)	0.91	0.36	2.32	NS
Nifedipine (*n* = 31)	8 (25.8)	3.83	1.53	9.57	*P* = 0.004
Stroke					
Benidipine (*n* = 66)	5 (7.6)	0.74	0.24	2.27	NS
Amlodipine (*n* = 45)	5 (11.1)	1.09	0.36	3.34	NS
Nifedipine (*n* = 31)	3 (9.7)	1.39	0.38	5.09	NS
ESRD					
Benidipine (*n* = 66)	4 (6.1)	0.38	0.12	1.17	NS
Amlodipine (*n* = 45)	7 (15.6)	1.22	0.45	3.30	NS
Nifedipine (*n* = 31)	5 (16.1)	2.85	0.97	8.44	NS

[a]The identification of risk factors for MACE used univariate Cox regression analysis.
Coronary angiography carried out between 1 January 1995 and 30 September 2006, and followed up on 1 January 2008.
Calcium channel blocker dose (mean ± SD): benidipine 6.7 ± 1.9 mg/day; amlodipine, 5.1 ± 1.2 mg/day; long-acting nifedipine, 40.6 ± 12.9 mg/day.
CI, confidence interval; NS, not statistically significant (*P* > 0.05).

percentage of patients without cardiac death was significantly higher in the benidipine (*P* < 0.001) and amlodipine (*P* = 0.013) groups than in the nifedipine group (Fig. 3B). Patients treated with benidipine or amlodipine showed significantly increased survival (*P* = 0.004 and *P* = 0.043 respectively), estimated from the total mortality, compared with those treated with nifedipine (Fig. 3C). A significant difference in the inhibitory effect against progression to ESRD was noted between nifedipine and benidipine (*P* = 0.034), although the difference between nifedipine and amlodipine was not statistically significant (Fig. 3D).

CHANGE IN BLOOD PRESSURE, HEART RATE AND PRP

The mean systolic/diastolic blood pressure for all 142 patients decreased significantly (*P* < 0.05) from 137 ± 20/74 ± 15 mmHg at the time of coronary angiography (baseline) to 129 ± 20/71 ± 12 mmHg at the last follow-up visit. The systolic, diastolic and mean blood pressures, heart rate and PRP at baseline and at the last follow-up visit for patients on each of the three CCBs are shown in Table 5.

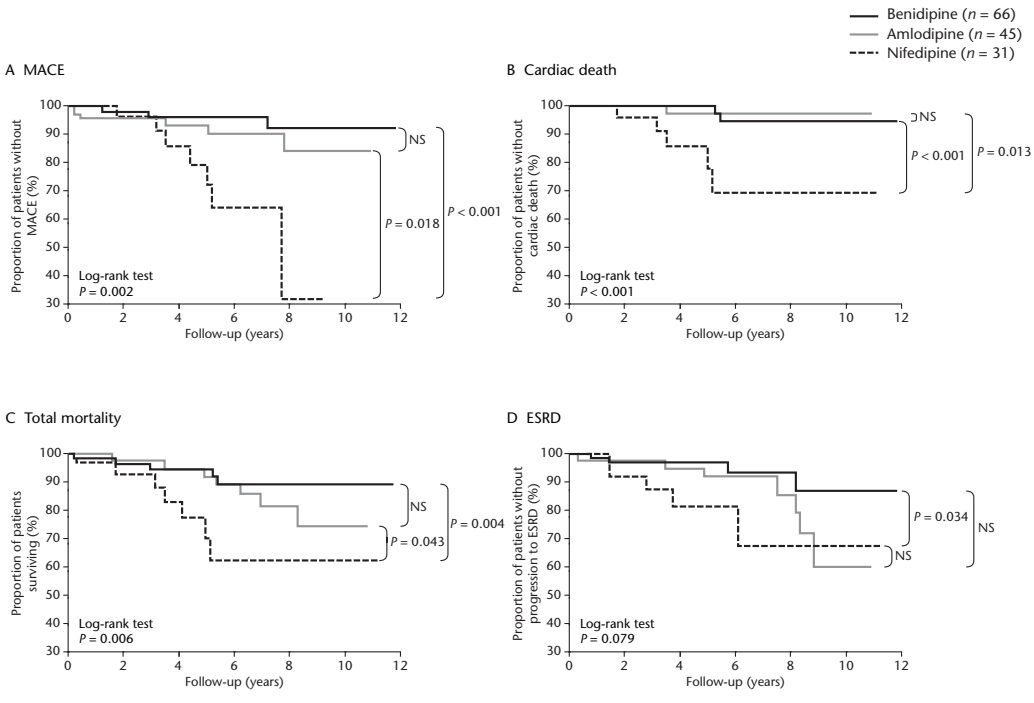

FIGURE 3: Influence of different calcium channel blockers on the time to: (A) a major adverse cardiovascular event (MACE); (B) cardiac death; (C) total mortality; or (D) end-stage renal disease (ESRD) after coronary angiography in patients with coronary artery disease and hypertension (mean ± SD dose: benidipine 6.7 ± 1.9 mg/day, amlodipine 5.1 ± 1.2 mg/day or long-acting nifedipine 40.6 ± 12.9 mg/day) (NS, not statistically significant [$P > 0.05$])

Significant lowering of systolic blood pressure at the last follow-up visit compared with baseline was observed for all three treatments ($P = 0.044$, $P = 0.044$ and $P = 0.016$ for benidipine, amlodipine and nifedipine, respectively), whereas the decrease from baseline in heart rate was only statistically significant in the benidipine group ($P = 0.004$). A significant decrease in the PRP was also observed in the benidipine ($P < 0.001$), amlodipine ($P = 0.046$) and nifedipine groups ($P = 0.028$).

Discussion

The incidence of MACE has been shown to rise with increasing severity of CKD.[16] This was confirmed by the present study, where the frequency of MACE was higher in patients with concurrent CKD. It is noteworthy that benidipine not only significantly suppressed progression to ESRD in CAD patients compared with nifedipine, but also reduced the incidence of MACE in CAD patients with CKD, the effects being more pronounced than those of nifedipine.

Studies have shown that benidipine is more useful than other CCBs for prophylaxis against MACE in patients with vasospastic angina.[10 – 12] Indeed, this may contribute to a reduction in the frequency of MACE in CAD patients because CAD in Japan is characterized by a high incidence of coronary

TABLE 5:
Blood pressure, heart rate and the pressure–rate product at the time of coronary angiography (baseline) compared with at the last follow-up visit in patients with coronary artery disease and hypertension, stratified according to calcium channel blocker treatment after hospital discharge

Treatment/parameter	Baseline	Last follow-up visit	Statistical significance[a]
Benidipine (n = 66)			
Systolic blood pressure (mmHg)	135.7 ± 23.3	128.7 ± 21.1	P = 0.044
Diastolic blood pressure (mmHg)	72.6 ± 14.7	70.3 ± 10.6	NS
Mean blood pressure (mmHg)	93.6 ± 16.0	89.8 ± 12.8	NS
Heart rate (beats/min)	76.6 ± 13.5	66.8 ± 10.5	P = 0.004
Pressure–rate product (mmHg beats/min)	10 298.1 ± 2956.4	7779.7 ± 1931.0	P < 0.001
Amlodipine (n = 45)			
Systolic blood pressure (mmHg)	137.7 ± 19.8	127.9 ± 22.7	P = 0.044
Diastolic blood pressure (mmHg)	77.3 ± 17.7	71.4 ± 13.3	NS
Mean blood pressure (mmHg)	97.4 ± 16.7	90.3 ± 15.8	NS
Heart rate (beats/min)	73.1 ± 13.2	72.1 ± 11.8	NS
Pressure–rate product (mmHg beats/min)	10 565.6 ± 2473.0	8647.2 ± 2378.5	P = 0.046
Nifedipine (n = 31)			
Systolic blood pressure (mmHg)	137.9 ± 15.5	128.2 ± 15.1	P = 0.016
Diastolic blood pressure (mmHg)	72.8 ± 10.0	70.1 ± 12.8	NS
Mean blood pressure (mmHg)	94.5 ± 10.2	89.5 ± 12.6	NS
Heart rate (beats/min)	74.3 ± 6.7	70.0 ± 11.3	NS
Pressure–rate product (mmHg beats/min)	10 671.1 ± 1868.7	8836.9 ± 1503.3	P = 0.028

[a]Comparison between baseline and last follow-up visit used the paired t-test.
Coronary angiography carried out between 1 January 1995 and 30 September 2006, and followed up on 1 January 2008.
Calcium channel blocker dose (mean ± SD): benidipine 6.7 ± 1.9 mg/day; amlodipine, 5.1 ± 1.2 mg/day; long-acting nifedipine, 40.6 ± 12.9 mg/day.
NS, not statistically significant (P > 0.05).

spasm (about 80%).[7,8] In the present study, benidipine was shown to reduce the incidence of MACE in CAD patients. According to the Japan Multicenter Investigation for Cardiovascular Diseases B (JMIC-B) Study Group, long-acting dihydropyridine CCBs can improve the prognosis in CAD patients,[17] particularly those with underlying hypertension.[5] One study in Japanese patients demonstrated a beneficial effect of benidipine on survival after myocardial infarction compared with the effects of short-acting nisoldipine and nifedipine.[18] The present study extended these findings, by demonstrating the protective effect of long-acting CCBs, such as benidipine and amlodipine, against MACE in hypertensive patients with CAD.

The better prognosis of CAD patients receiving benidipine compared with those receiving nifedipine could be attributable to the following actions of benidipine. First, benidipine acts more selectively on the coronary vessels than nifedipine.[19] This selective action on the coronary vessels increases the myocardial oxygen supply, resulting in a potent inhibition of myocardial damage. Secondly, benidipine exerts a vasodilatory effect of slower onset than nifedipine,[20] which makes it less liable to enhance sympathetic nerve activity than

the other CCBs, including nifedipine.[21] Thirdly, benidipine is a T-type CCB, possibly more potent than nifedipine and other CCBs.[22] T-type calcium channels in the myocardium are known to affect the heart rate. In the present study, the significant decrease in heart rate induced by benidipine may have resulted in a reduction of the incidence of MACE. Finally, benidipine has been shown to produce a greater degree of enhancement of nitric oxide production[23] and exert more pronounced antioxidant activity[24] than other CCBs.

There were several limitations to the present study. First, this was a retrospective study, as data for all included patients with hypertension and CAD were extracted from a database of consecutive patients who underwent coronary angiography. Thus, no definitive conclusions can be made as to the effect of CCBs in preventing MACE. Secondly, the number of patients treated with a drug-eluting stent was relatively low, as most of the patients were enrolled early in the screening period from 1995 to 2006. It is possible, based on the results of the present study, that the effects of CCBs might differ between patients with drug-eluting and bare metal stents. A future large-scale trial will be necessary to arrive at any definitive conclusions on this subject.

In conclusion, CKD was confirmed to be a significant risk factor for cardiovascular events in hypertensive patients with CAD. These results demonstrate that benidipine as well as amlodipine might contribute to reducing the frequency of MACE in hypertensive patients with CAD, particularly among those with concurrent CKD, which was identified as a significant risk factor for MACE.

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Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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