Amlodipine in the Prevention and Treatment of Cardiovascular Disease

a report by
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Despite the presence of an artificial debate developed in the past decade[1,2] focusing on calcium channel blockers and their role in the prevention and treatment of cardiovascular diseases, a huge amount of evidence has been created favouring this class of agents in the treatment of hypertension and associated cardiovascular diseases.[3] Calcium channel blockers are divided into three classes, the most popular of which are the dihydropyridines. There is more evidence from clinical trials for amlodipine than for the other molecules in this class; these trials included the highest number of hypertensives and patients with coronary artery disease. While the 7th Report of the US Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[4] (JNC VII) recommended the use of diuretics as the preferred class of drugs for treatment of hypertension, international clinical guidelines on antihypertensive treatment from the World Health Organization (WHO)/International Society of Hypertension (ISH)[5] in 1999 and the recently updated guidelines from the European Society of Hypertension (ESH)/ European Society of Cardiology (ESH)[6] both recommended the use of long-acting calcium channel blockers as one of the first-line antihypertensive drug classes, and emphasised their capacity to be used in combination with most of the other antihypertensive drug classes, including thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists, in order to better achieve blood pressure goals. This article reviews the most important studies carried out with amlodipine in hypertensives and patients with coronary heart disease, as well as complementary data with other calcium channel blockers, indicating a clear and unequivocal beneficial effect in the prevention of atherosclerosis and cardiovascular events.

Amlodipine in Hypertension

The role of amlodipine as an antihypertensive agent was clearly stated more than 15 years ago. At that time several reviews had been published describing its mechanism of action and its efficacy and tolerability in treating hypertensives when used either as monotherapy or in combination with other antihypertensive agents.[7,8] However, the biggest impact occurred in the last six years with the publication of results of clinical trials with mortality and morbidity end-points in which amlodipine was used as part of therapy. These trials were the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[9] the Valsartan Antihypertensive Long-term Use Evaluation (VALUE)[10] and the AngloScandinavian Cardiac Outcome Trial (ASCOT).[11] ALLHAT is the largest trial of antihypertensive therapy conducted to date. It included 42,418 hypertensive patients over the age of 55 years who had an additional cardiovascular risk factor. Patients were randomised to receive antihypertensive treatment based on chlorthalidone, amlodipine, lisinopril or doxazosin, although the latter group was halted prematurely.[12] After six years of follow-up, the primary outcome (fatal coronary heart disease or non-fatal myocardial infarction) occurred in 11.3% of amlodipine-treated patients, 11.4% of lisinopril-treated patients and 11.5% of chlorthalidone-treated patients (relative risk (RR) of amlodipine versus chlorthalidone 0.98, 95% confidence interval (CI) 0.90–1.07).

Despite this lack of difference in the primary end-point, the ALLHAT investigators argued that chlorthalidone was superior to amlodipine or lisinopril in the treatment of hypertension due to a better outcome in at least one secondary end-point. This argument also influenced the JNC VII guidelines,[4] which, as previously mentioned, chose thiazide diuretics as first-class therapy for "most" hypertensives. In ALLHAT, the comparison between amlodipine and chlorthalidone showed that amlodipine tended to decrease total mortality (RR 0.96, 95% CI 0.89–1.02), stroke (RR 0.93, 95% CI 0.82–1.06) and peripheral artery disease requiring treatment or hospitalisation (RR 0.87, 95% CI 0.75–1.01), even though systolic blood pressure was maintained 1–2mmHg higher in the amlodipine group throughout the study. The only difference favouring chlorthalidone over amlodipine was the incidence of heart failure, which was between 25 and 52% more frequent in the amlodipine group. However, ALLHAT was not prospectively powered to look for heart failure as an end-point and heart failure was not defined by traditional criteria. Oedema was not well defined, occurred more commonly in the first study year and was probably influenced by shifting patients abruptly from rational drug regimens to the study drugs on the first day.[13] Other differences between amlodipine and chlortalidone were seen at biochemical levels. At two years of follow-up, mean levels of cholesterol (202.5 versus 205.3mg/dl) and plasma fasting glucose (122.4 versus 127.6mg/dl) were significantly lower in the amlodipine group than in the chlorthalidone group, and these differences were maintained at four years. Moreover, the proportion of patients who developed dyslipidaemia, defined by total cholesterol >240mg/dl, or hyperglycaemia, defined by fasting glucose >125mg/dl, was lower in the amlodipine group at two-year follow-up.

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The VALUE trial[10] included 15,245 high-risk hypertensive patients over 50 years of age who were randomised to antihypertensive treatment based on either valsartan or amlodipine, with the addition of hydrochlorothiazide and open antihypertensive therapy when required. The primary outcome was cardiac morbidity and mortality. After a mean follow-up of 4.2 years, the trial failed to show the superiority of valsartan over amlodipine in the primary end-point (hazard ratio (HR) 1.04, 95% CI 0.94–1.15). In contrast, amlodipine was superior to valsartan in the prevention of myocardial infarction (19%; p=0.02) and stroke (15%; p=0.08). The VALUE trial showed important differences in the blood-pressure reduction achieved by the two treatment regimens. This was illustrated by both the percentage of patients at each step of treatment and mean blood pressure in each group at every evaluation. The percentage of patients at the first step of treatment (80mg valsartan or 5mg amlodipine) was 15.9 and 20.8%, respectively. In contrast, the proportion of patients requiring other antihypertensive drugs in addition to the maximum treatment study dosage (160mg valsartan or 10mg amlodipine plus 25mg hydrochlorothiazide) was 23.0% in the valsartan group and 16.8% in the amlodipine group. Blood-pressure differences were especially apparent during the first part of the study (4/2.1mmHg in the first month) and remained at more than 1mmHg throughout follow-up.

In order to separate the blood-pressure-dependent and -independent effects of antihypertensive treatment, the VALUE investigators carried out a special case-control analysis, choosing more than 5,000 pairs of patients matched for age, sex, risk and, especially, systolic blood pressure.[14] Using this approach, differences in the cardiovascular end-point that favoured amlodipine in the main analysis disappeared. However, the main conclusion of the VALUE trial was that early blood-pressure reduction was clearly the most important issue for the prevention of cardiovascular disease, at least in high-risk hypertensives, and this was achieved earlier and more effectively by amlodipine treatment. Another important aspect of the VALUE results was the effectiveness of the combination of amlodipine and thiazide diuretic. Although it was previously thought that calcium channel blockers–diuretic combinations were not as effective as diuretics combined with beta-blockers or renin-angiotensin inhibitors due to the complementary mechanisms of action, the results of VALUE demonstrated a higher potency of amlodipine–hydrochlorothiazide than valsartan–hydrochlorothiazide. Since then, new hypertension guidelines have emphasised the use of such a combination for blood-pressure control in hypertensives.[6]

The most recent trial published in hypertension with amlodipine is the ASCOT trial.[11] A total of 19,257 hypertensive patients aged 40–79 years with at least three other cardiovascular risk factors received amlodipine (most with added perindopril) or atenolol (most with added thiazide). The primary outcome was cardiac morbidity and mortality. The ASCOT trial was halted prematurely by the data safety monitoring board on the grounds that excess total mortality was observed in one of the treatment groups. Thus, although no significant differences were observed in the primary objective (HR of amlodipine compared with atenolol 0.90, 95% CI 0.79–1.02), significant reductions in almost all secondary end-points – such as all-cause mortality (11%), cardiovascular mortality (24%), stroke (23%), total coronary end-points (13%) and total number of cardiovascular events and procedures (16%) – tertiary end-points – such as unstable angina (32%), peripheral artery disease (35%) and development of diabetes mellitus (21%) or renal impairment (15%) – and *post hoc* end-points – such as the combination of myocardial infarction, stroke and cardiovascular death (16%) – favoured amlodipine treatment. This wide range of beneficial effects observed in the amlodipine group was accompanied by better and earlier blood-pressure control in patients receiving such treatment. Wider differences between treatment groups were observed at three months (5.9mmHg systolic/2.4mmHg diastolic) and were maintained throughout the study, with an average of 2.7mmHg in systolic BP and 1.9mmHg in diastolic BP.

Other Calcium Channel Blockers in Hypertension

Three studies have compared other calcium channel blockers against diuretics and/or beta-blockers in hypertensive patients: The Nordic Diltiazem (NORDIL) study,[15] the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT)[16] and the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE).[17] In the NORDIL study,[15] diltiazem was compared with conventional antihypertensive therapy (diuretics and/or beta-blockers) in more than 10,000 hypertensive patients over the age of 50 years. Although diltiazem reduced systolic blood pressure by 3mmHg less than conventional therapy, no differences were observed in the primary objective (a combination of stroke, myocardial infarction and cardiovascular death). The total number of strokes was significantly reduced in the diltiazem group (RR 0.80; p=0.04) with respect to conventional therapy. Simultaneously, the INSIGHT trial[16] compared long-acting nifedipine against a combination of two diuretics (hydrochlorothiazide and amiloride) in more than 6,000 high-risk hypertensives. The occurrence of the primary outcome – a combination of stroke, myocardial infarction, heart failure and cardiovascular death – did not differ significantly between nifedipine- or diuretic-treated patients (RR 1.10; p=0.35). The third study, the CONVINCE trial,[17] included a total of 16,476 hypertensives with an additional cardiovascular risk factor treated with controlled-onset extended-release verapamil or conventional therapy (atenolol or hydrochlorothiazide). No differences in the primary objective (stroke, myocardial infarction or cardiovascular death) were seen between groups (HR of verapamil versus conventional treatment 1.04; 95% CI 0.88–1.18). However, the trial was planned as a non-inferiority study, and the upper limit of the 95% CI (1.18) exceeded the pre-specified boundary of 1.16, meaning that non-inferiority could not be demonstrated. The study also had two important limitations. First, because obesity was the most frequent associated cardiovascular risk factor (50% of patients), the overall risk of hypertensive patients included was probably less than expected. Second, the study was prematurely halted due to administrative reasons before a sufficient number of events occurred (fewer than one-third of the planned number). These two important flaws make it difficult to regard the CONVINCE trial as conclusive.

Amlodipine and Prevention of Atherosclerosis

Amlodipine treatment has been associated with an impairment in the progression of atherosclerosis at both coronary and carotid levels. First, in the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT),[18] 825 patients with angiographically documented coronary artery disease were randomised to amlodipine or placebo for 36 months. The primary outcome was the change in diameter of coronary segments with stenosis, and a secondary measure was the effect on carotid atherosclerosis measured by ultrasonography. Without differences in the change in coronary diameter, patients treated with amlodipine reduced the progression of carotid atherosclerosis, as measured by the change in the intima-media thickness, compared with those treated with placebo. Moreover, amlodipine treatment was associated with fewer cases of unstable angina and coronary revascularisation. Second, the Comparison of Amlodipine versus Enalapril to

Limit Occurrences of Thrombosis (CAMELOT)[19] study included 1,991 patients with angiographically documented coronary disease (>20% stenosis) who were randomised to amlodipine, enalapril or placebo. The primary end-point was a combination of fatal and non-fatal cardiovascular events. In the CAMELOT trial, amlodipine significantly reduced the rate of the primary end-point compared with placebo (HR 0.69, 95% CI 0.54–0.88). The rate reductions of enalapril against placebo (15%) or amlodipine against enalapril (19%) were not statistically significant. The CAMELOT trial included a substudy in 274 patients with measurement of coronary atherosclerosis progression by intravascular ultrasound (IVUS). The percentage atheroma volume increased by 3.1% in the placebo group (p=0.001 from baseline), by 1.9% in the enalapril group (p=0.08 from baseline) and by 1.3 in the amlodipine group (p=0.31 from baseline).

Other mechanisms of atherosclerosis, including oxidative stress, nitric oxide endothelial production and low-density lipoprotein (LDL) oxidation and aggregation, have also been shown to be modified by amlodipine *in vivo* or *in vitro*.[20] Specifically, both *in vitro* and *in vivo* studies have shown that amlodipine inhibited oxidative damage to lipids associated with cellular membranes and lipoprotein particles.[21,22] This antioxidant activity of amlodipine was attributed to both its high lipophilicity and its chemical structure, which facilitated proton-donating and resonance–stabilisation mechanisms that quench the free-radical reaction. Amlodipine was also able to enhance nitric oxide production in the absence of shear stress changes.[23] Finally, other vascular actions of amlodipine included inhibition of vascular smooth muscle cell proliferation[24] and matrix metalloproteinase modulation,[25] all actions that can be related with antiatherosclerotic effects.[20] More recently, the effects of antihypertensive treatment on the elastic properties of conduit arteries have been proposed as a marker of the beneficial effect. The effects of amlodipine treatment were evaluated in a subgroup of the aforementioned ASCOT trial. The Conduit Artery Function Evaluation (CAFE)[26] study recruited 2,199 patients in five ASCOT centres. In addition to brachial blood pressure, central blood pressure was measured at baseline and in each follow-up visit by means of radial applanation tonometry. Without significant differences in brachial blood pressure between the amlodipine and atenolol groups, central aortic pressure was reduced by amlodipine in comparison with atenolol (mean difference in central systolic pressure 4.3mmHg, in central pulse pressure 3.0mmHg, in central diastolic pressure 1.4mmHg and in augmentation index 6%, all of which are statistically significant). Moreover, in a multivariate analysis the authors found a relationship between the reduction of central pressures and the favourable outcome in amlodipine-treated patients.

Conclusion

The cardiovascular protection provided by long-acting calcium channel blockers, particularly amlodipine, in hypertensive patients is at least as effective as that obtained with other antihypertensive agents, including conventional treatment with diuretics or beta-blockers[27] or newer drugs such as angiotensin-receptor blockers.[28] In addition, amlodipine can be safely combined with other antihypertensive drug classes, including diuretics,[6,10] producing the early and effective blood-pressure control that is essential for the cardiovascular protection of high-risk patients. As most of these patients will require a combination of at least two hypertensive drugs to promote adequate blood pressure control, amlodipine represents one of the preferred drugs for this combination. Finally, its association with renin-angiotensin-system-blocking agents, such as angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, may yield additional benefits in cardiovascular protection[11] and reduce the development of new-onset type 2 diabetes;[29] this also has important prognostic implications.[30] ■

1. Psaty BM, Heckbert SR, Koepsell TD, et al., The risk of myocardial infarction associated with antihypertensive drug therapies, *JAMA*, 1995;274:620–25.
2. Pahor M, Psaty BM, Alderman MH, et al., Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials, *Lancet*, 2000;356:1949–54.
3. De la Sierra A, Ruilope LM, Are calcium channel blockers first-line drugs for the treatment of hypertension and cardiovascular disease?, *Curr Hypertens Rev*, 2007;3:9–13.
4. Chobanian AV, et al., The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report, *JAMA*, 2003;289:2560–72.
5. Guidelines Subcommittee, 1999 World Health Organization–International Society of Hypertension Guidelines for the management of hypertension, *J Hypertens*, 1999;17:151–83.
6. Mancia G, De, et al., 2007 guidelines for the management of arterial hypertension, *J Hypertens*, 2007;25:1105–87.
7. Murdoch D, Heel RC, Amlodipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease, *Drugs*, 1991;41:478–505.
8. Haria M, Wagstaff AJ, Amlodipine. A reappraisal of its pharmacological properties and therapeutic use in cardiovascular disease, *Drugs*, 1995;50:560–86.
9. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic, *JAMA*, 2002;288:2981–97.
10. Julius S, Kjeldsen SE, Weber M, et al., Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial, *Lancet*, 2004;363:2022–31.
11. Dahlöf B, Sever PS, Poulter NR, et al., Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial, *Lancet*, 2005;366:895–906.
12. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlortalidone. The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), *JAMA*, 2000;283:1967–75.
13. Standridge JB, A family physician questions the conclusion from ALLHAT, *Am J Hypertens*, 2004;17:361–5.
14. Weber MA, Julius S, et al., Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE trial, *Lancet*, 2004;363:2049–51.
15. Hansson L, Hedner T, et al., Randomised trial of effects of calcium antagonists compared with diuretics and β-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study, *Lancet*, 2000;356:359–65.
16. Brown MJ, Palmer CR, Castaigne A, et al., Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT), *Lancet*, 2000;356:366–72.
17. Black HR, Elliot WJ, Grandist G, et al., Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) trial, *JAMA*, 2003;289:2073–82.
18. Pitt B, Byington RP, Furberg CD, et al., Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events, *Circulation*, 2000;102:1503–10.
19. Nissen SE, Tuzcu EM, Libby P, et al., for the CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure. The CAMELOT study: a randomized controlled trial, *JAMA*, 2004;292:2217–26.
20. Mason RP, Marche P, Hintze TH, Novel vascular biology of third-generation L-type calcium channel antagonists, *Arterioscler Thromb Vasc Biol*, 2003;23:2155–63.
21. Mason RP, Walter MF, Trumbore MW, et al., Membrane antioxidant effects of the charged dihydropyridine calcium antagonist amlodipine, *J Mol Cell Cardiol*, 1999;31:275–81.
22. Phillips JE, Mason RP, Inhibition of oxidized LDL aggregation with a charged calcium antagonist amlodipine: role of electrostatic interactions, *Atherosclerosis*, 2003;168:239–44.
23. Zhang X, Hintze TH, Amlodipine releases nitric oxide from canine coronary microvessels: an unexpected mechanism of action of a calcium channel-blocking agent, *Circulation*, 1998;97:576–80.
24. Stepien O, et al., Amlodipine inhibition of serum-, thrombin-, or fibroblast growth factor-induced vascular smooth-muscle cell proliferation, *J Cardiovasc Pharmacol*, 1998;31:786–93.
25. Roth M, Eickelberg O, Köhler E, et al., Ca^{2+} channel blockers modulate metabolism of collagens within the extracellular matrix, *Proc Natl Acad Sci U S A*, 1996;93:5478–82.
26. Williams B, Lacy PS, Thom SM, et al., for the CAFE Investigators. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes. Principal results of the Conduit Artery Function Evaluation (CAFE) Study, *Circulation*, 2006;113:1213–25.
27. Blood Pressure Lowering Treatment Trialists' Collaboration, Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials, *Lancet*, 2003;362:1527–35.
28. Wang JG, Li Y, Franklin SS, Safar M, Prevention of stroke and myocardial infarction by amlodipine and angiotensin receptor blockers: a quantitative overview, *Hypertension*, 2007;50:181–8.
29. Elliott WJ, Meyer PM, Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis, *Lancet*, 2007;369:201–7.
30. Aksnes TA, Kjeldsen SE, Rostrup M, et al., Impact of new-onset diabetes mellitus on cardiac outcomes in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial population, *Hypertension*, 2007;50:467–73.