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\(^1\), 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.\(^2\) Calcium channel blockers are divided into three classes, the most popular of which are the dihydropyridines. There is more evidence from clinical trials for amlo dipine 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 (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)\(^3\) in 1999 and the recently updated guidelines from the European Society of Hypertension (ESH)/European Society of Cardiology (ESC)\(^4\) 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 amlo dipine 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 amlo dipine 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.\(^5\) 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 amlo dipine was used as part of therapy. These trials were the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),\(^6\) the Valsartan Antihypertensive Long-term Use Evaluation (VALUE)\(^7\) and the AngloScandinavian Cardiac Outcome Trial (ASCOT).\(^8\) 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, amlo dipine, lisinopril or doxazosin, although the latter group was halted prematurely.\(^9\) After six years of follow-up, the primary outcome (fatal coronary heart disease or non-fatal myocardial infarction) occurred in 11.3% of amlo dipine-treated patients, 11.4% of lisinopril-treated patients and 11.5% of chlorthalidone-treated patients (relative risk (RR) of amlo dipine 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 amlo dipine 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 amlo dipine and chlorthalidone showed that amlo dipine 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 amlo dipine group throughout the study. The only difference favouring chlorthalidone over amlo dipine was the incidence of heart failure, which was between 25 and 52% more frequent in the amlo dipine 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.\(^1\) Other differences between amlo dipine and chlorthalidone 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 amlo dipine 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 amlo dipine group at two-year follow-up.
The VALUE trial 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 (42.1mmHg 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. 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.

The most recent trial published in hypertension with amlodipine is the ASCOT trial. 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.
Hypertension Calcium Channel Blockers

Limit Occurrences of Thrombosis (CAMELOT) study included 1,991 patients with angiographically documented coronary disease (>20% stenosis) who were randomised to amloidipine, enalapril or placebo. The primary end-point was a combination of fatal and non-fatal cardiovascular events. In the CAMELOT trial, amloidipine 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%) and amloidipine 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 amloidipine 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 amloidipine in vivo or in vitro. Specifically, both in vitro and in vivo studies have shown that amloidipine inhibited oxidative damage to lipids associated with cellular membranes and lipoprotein particles. This antioxidant activity of amloidipine 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. Amloidipine was also able to enhance nitric oxide production in the absence of shear stress changes. Finally, other vascular actions of amloidipine included inhibition of vascular smooth muscle cell proliferation and matrix metalloproteinase modulation, all actions that can be related with antiatherosclerotic effects. 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 amloidipine treatment were evaluated in a subgroup of the aforementioned ASCOT trial. The Conduit Artery Function Evaluation (CAFE) 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 amloidipine and atenolol groups, central aortic pressure was reduced by amloidipine in comparison with atenolol (mean difference in central systolic pressure 4.3 mmHg, in central pulse pressure 3.0 mmHg, in central diastolic pressure 1.4 mmHg 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 amloidipine-treated patients.

Conclusion
The cardiovascular protection provided by long-acting calcium channel blockers, particularly amloidipine, in hypertensive patients is at least as effective as that obtained with other antihypertensive agents, including conventional treatment with diuretics or beta-blockers or newer drugs such as angiotensin-receptor blockers. In addition, amloidipine can be safely combined with other antihypertensive drug classes, including diuretics, 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, amloidipine 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 and reduce the development of new-onset type 2 diabetes.