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REVIEW

Efficacy and Safety of Single-Pill Amlodipine Besylate/Atorvastatin Calcium in the Management of Hypertension and Angina

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Abstract: Hypertension and hypercholesterolemia are two of the main causes of disease burden worldwide. Both conditions are related, and the prevalence of hypercholesterolemia is higher in hypertensive patients and vice versa. Current guidelines agree that the aim of treatment should not only be to control just one risk factor, but to reduce overall cardiovascular risk through a multifactorial intervention, treating all risk factors and conditions as associated. Nevertheless, current control rates are far from optimal. The combination of amlodipine and atorvastatin has been shown to effectively reduce both blood pressure and LDL-cholesterol levels with a good tolerability profile. This in turn has led to a more intense reduction in coronary events than with other regimens, as observed in the ASCOT trial. Furthermore, simplification of treatment can improve adherence. In this context, fixed combinations help to achieve this goal. This paper updates published data on the combination of amlodipine and atorvastatin.

Keywords: amlodipine, atorvastatin, fixed combination, hypertension, hypercholesterolemia

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Importance of Coronary Heart Disease

Cardiovascular disease is the most common cause of morbidity and mortality worldwide, not only in Western countries but also in newly industrialized nations, with coronary heart disease (CHD) being the most frequent type.[1] In Europe, cardiovascular disease was the cause of more than four million deaths (nearly two million in the European Union) in 2000.[2] Moreover, cardiovascular disease is the most important cause of hospitalization and in 2002 was responsible for an average rate of 2,557 admissions per 100,000 people (695 per 100,000 due to CHD).[1,2] Consequently, these high rates imply that cardiovascular disease is associated with higher costs.[3] In the United States, data from the National Health and Nutrition Examination Survey (NHANES) indicate that more than 13 million people have CHD and that prevalence increases with age. Thus, prevalence ranges from 7% at age 40 to 49 years to 22% at 70 to 79 years in men, and from 5% to 15% in women.[4] Ageing of the population and availability of better treatment for acute coronary syndromes make it likely that the prevalence of CHD will increase in the coming years.[5]

Mortality rates for CHD have decreased by 25% in most developed countries since 1975, although this reduction has slowed since 1990,[6,7] thanks to better treatments for acute events and better control of cardiovascular risk factors.[8,9] For example, between 1994 and 2005, CHD mortality rates decreased in Ontario, Canada, due mainly to trends in risk factors and improved medical treatment, each accounting for about half of the decrease.[9] By contrast, in developing countries (including Latin America, the Middle East, China, India, and Sub-Saharan Africa), mortality from CHD is increasing, likely due to social and economic changes, physical inactivity, an increase in cigarette smoking, and Westernized diets.[10]

Hypertension, Low-Density Lipoprotein Cholesterol and Coronary Heart Disease

Hypertension, smoking, and high cholesterol levels are the major causes of disease burden in both developing and developed countries.[11] In fact, as MRFIT (Multiple Risk Factor Intervention Trial) showed, there is a strong graded relationship between total serum cholesterol levels above 180 mg/dL, systolic blood pressure (BP) above 110 mmHg, diastolic BP above 70 mmHg, and mortality due to CHD.[12] As a result, smoking cessation and achieving BP and cholesterol control objectives should be the main goals for improving survival.

Arterial hypertension is a common major risk factor for cerebrovascular, cardiovascular, and renal diseases, and its prevalence is estimated at 30% in the general population and about 65% in the elderly.[13–15] Hypertension is thought to be responsible for one in every four deaths for any reason and for one in every 2.5 cardiovascular deaths.[16] Although attaining BP goals is crucial in the general hypertensive population, it is even more important in high-risk patients, such as those with ischemic heart disease. The INVEST (International Verapamil SR-Trandolapril) trial, which included more than 22,000 patients with hypertension and ischemic heart disease, revealed a considerable reduction in cardiovascular risk as the number of visits with uncontrolled BP increased, irrespective of baseline clinical characteristics and mean on-treatment BP.[17] However, treating hypertension is not enough; it is also important to achieve BP goals. Thus, one systematic review showed that hypertensive patients who achieved BP goals had a 42% reduction in the risk of stroke ($P < 0.0001$) and a 14% reduction in the risk of CHD, compared with patients who were treated but not adequately controlled.[18]

Several epidemiologic studies have clearly shown that high levels of low-density lipoprotein cholesterol (LDL-C) are a major cause of CHD. Furthermore, clinical trials strongly demonstrate that LDL-lowering therapy reduces the risk of developing CHD.[19–24] For example, in the Heart Protection Study, 20,536 UK adults aged 40–80 years with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive 40 mg of simvastatin daily or a matching placebo.[21] The main results of this study showed that adding simvastatin to existing treatments safely resulted in substantial additional benefits, irrespective of initial cholesterol concentrations, and that it reduced the rates of myocardial infarction, stroke, and revascularization by about one-quarter.[21] Current recommendations from the National Cholesterol Education Program Adult Treatment Panel III suggest starting drug therapy for patients with an LDL-C above 100 mg/dL and CHD or equivalent diseases, and setting an additional goal of

achieving LDL-C below 70 mg/dL, especially in very high-risk patients.[25]

The prevalence of hypercholesterolemia is higher in the hypertensive population and vice versa.[26,27] Thus, in the PRESCOT (Prevención Cardiovascular en España en Atención Primaria: Intervención Sobre el Colesterol en Hipertensión) study, nearly three-quarters of 13,000 hypertensive patients attended daily by general practitioners in Spain had hypercholesterolemia and, conversely, that about 50% of hypercholesterolemic patients also attended in Spanish primary care centers were hypertensive.[26,27] Although high BP levels and high cholesterol levels alone increase the likelihood of developing CHD, co-occurrence of both increases this risk exponentially.

Current guidelines agree that the aim of treatment should not only be to control a single risk factor, but also to reduce overall cardiovascular risk through a multifactorial intervention, treating all risk factors and conditions as associated.[28] However, when current control rates are analyzed, the results are discouraging. Thus, in a hypertensive population in which 12.6% belonged to the low-risk group, 45% to the medium-risk group, and 42.4% to the high-risk group, the control rates decreased as cardiovascular risk increased. Control of BP ranged from 37.5% in low-risk patients to 15.4% in high-risk patients; control of LDL-C ranged from 65.6% in low-risk patients to 12.3% in high-risk patients. When both risk factors were analyzed together, the percentages decreased dramatically, to 25.8% for low-risk patients and 2.7% for high-risk patients ($P < 0.0001$ for the trend in all the cases).[27] In another cross-sectional and multicenter survey designed to assess the clinical management of hypertensive outpatients with chronic ischemic heart disease attended by cardiologists, in whom 78.4% of the patients had dyslipidemia, about 40% of patients attained the BP objectives and 30% of the dyslipidemic subgroup attained the LDL-C objectives (Fig. 1).[29] These data show much room for improvement and a need for new approaches to improve results.

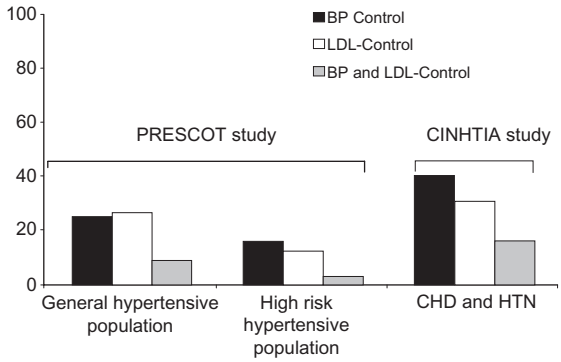

Figure 1. Blood pressure and LDL-cholesterol control rates in different populations (adapted from references 27 and 29).
Note: *The control rates in high-risk hypertensive patients were lower than for the comparators (overall, $P < 0.0001$).
Abbreviations: BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; CHD, coronary heart disease; HTN, hypertension; PRESCOT, Prevención Cardiovascular en España en Atención Primaria: Intervención Sobre el Colesterol en Hipertensión; CINHTIA, Cardiopatia Isquemica croNica e Hiper ension Arterial en la practica clinica en España.

The Importance of Combined Therapy

Combined therapy has many advantages, mainly improved adherence and increased efficacy with a good tolerability profile.[30] The combination of drugs with different mechanisms of action can block counter-regulatory mechanisms and enhance efficacy beyond the additive response of each drug alone. Moreover, combined therapy is associated with a lower incidence of side effects due to possible compensatory responses and, in many cases, the lower doses used.[30] In fact, combined therapy is the treatment of choice in many patients with chronic diseases such as hypertension, diabetes, or dyslipidemia.[1,30,31]

However, adherence to therapy is often poor in patients with chronic disease, due to a number of factors, including complexity of treatment, lack of efficacy, side effects, knowledge of disease, and cost.[32,33] As a result, treatment must be simplified to improve adherence. Medications can be combined as two drugs in a single tablet (fixed combination) or in separate tablets (free combination). Although the fixed dose of the combination components limits the flexibility of upward and downward treatment strategies, fixed combinations reduce the pill burden, thus favoring adherence and control of risk factors during follow-up.[30,34–36] In their meta-analysis, Bangalore et al[36] compared the effects of fixed-dose combinations with a free-drug regimen to improve adherence. To be included, studies had to have compared fixed-dose combinations with free-drug components of the regimen administered separately. Finally, nine studies fulfilled the inclusion criteria (two studies in tuberculosis, four in hypertension, one in human immunodeficiency virus infection, and two in diabetes). Nearly 12,000 patients on a fixed-dose combination were compared with more than 8,000 patients on a free-drug regimen. The fixed-dose

combination resulted in a 26% decrease in the risk of non-adherence compared with the free-drug regimen (pooled relative risk 0.74; 95% confidence interval [CI], 0.69–0.80; $P < 0.0001$).

These data indicate that the only way to reduce cardiovascular burden, particularly in high-risk patients, is by simultaneously treating different risk factors and that fixed combinations have several advantages over free combinations. In this context, the fixed combination amlodipine/atorvastatin may improve control of risk factors.

Pharmacology of Amlodipine and Atorvastatin

Amlodipine besylate is a third-generation dihydropyridine calcium channel blocker. It inhibits calcium entry through voltage-gated transmembrane L-type channels, leading to a reduction in intracellular calcium and promoting smooth muscle relaxation and a decrease in BP.[37] Amlodipine is eliminated slowly (elimination half-life of 40–60 h) and has high oral bioavailability (60%–80%). It accumulates to a steady-state concentration with once-daily administration over a period of 1–1.5 weeks. Onset of effect is gradual after oral administration. Amlodipine (monotherapy or combined therapy) has been approved for the treatment of hypertension and both vasospastic and chronic stable angina.[32,37]

Atorvastatin calcium is a synthetic lipid-lowering drug. It inhibits the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA to mevalonate. This leads to upregulation of LDL-C receptors in the liver, resulting in enhanced clearance of LDL.[32] Atorvastatin is absorbed rapidly after oral administration. Maximum plasma concentrations occur within 1–2 hours, and, notably, the extent of absorption increases in proportion to dose. The absolute bioavailability of atorvastatin is approximately 14% and it is ≥98% bound to plasma proteins. Atorvastatin is metabolized by cytochrome P450 3A4. Its mean plasma elimination half-life in humans is about 14 hours.[32,38]

After oral administration, the fixed combination amlodipine/atorvastatin exhibits a similar rate and extent of absorption to that observed when each drug is administered alone.[39] Since the half-lives of amlodipine and atorvastatin allow once-daily dosing and both can be administered at any time of day, irrespective of food intake, both drugs can be combined into a single pill to reduce cardiovascular risk.[40]

Findings for Amlodipine

Several trials have shown the benefits of using amlodipine to treat patients with hypertension or CHD. ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm) compared the effect on non-fatal myocardial infarction and fatal CHD of combinations of atenolol with a thiazide versus amlodipine with perindopril in nearly 20,000 hypertensive patients aged 40–79 years with at least three other cardiovascular risk factors.[41] The study was stopped prematurely after a median 5.5 years' follow-up. Compared with the atenolol-based regimen, although not significant, fewer subjects on the amlodipine-based regimen were affected by the primary endpoint (HR, 0.90; 95% CI, 0.79–1.02; $P = 0.1052$). However, fatal or non-fatal stroke (HR, 0.7; 95% CI, 0.66–0.89; $P = 0.0003$), total cardiovascular events and procedures (HR, 0.84; 95% CI, 0.78–0.90; $P < 0.0001$), and all-cause mortality (HR, 0.89; 95% CI, 0.81–0.99; $P = 0.025$) were significantly reduced by amlodipine-based regimen. However, the differences were not significant. Moreover, the incidence of new-onset diabetes was lower with the amlodipine-based regimen (HR, 0.70; 95% CI, 0.63–0.78; $P < 0.0001$). ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)[42] compared lisinopril-based therapy with amlodipine-based therapy in hypertensive patients and found that the risks for coronary events were similar; however, the risks were higher for stroke, combined cardiovascular disease, gastrointestinal bleeding, and angioedema, and lower for heart failure. It is likely that some, but suggestively not all, of these differences may be explained by less effective BP control in the lisinopril arm. ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension)[43] was the first randomized clinical trial to compare 2 fixed antihypertensive combinations–the fixed combination of benazepril (an angiotensin-converting-enzyme inhibitor) with amlodipine and benazepril with hydrochlorothiazide–in more than 11,000 high-risk hypertensive patients. The trial was terminated early after a mean follow-up of 36 months. Mean BP after dose adjustment was 131.6/73.3 mmHg in the benazepril/amlodipine

group and 132.5/74.4 mmHg in the benazepril/hydrochlorothiazide group. However, compared with patients taking benazepril/hydrochlorothiazide, patients treated with benazepril/amlodipine exhibited a 19.6% reduction (HR, 0.80; 95% CI, 0.72–0.90; $P < 0.001$) in the composite endpoint of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization.

Other trials have analyzed the benefits of treating CHD patients with amlodipine.[44,45] PREVENT (Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial)[44] was a multicenter, randomized, placebo-controlled, double-masked clinical trial designed to test whether amlodipine would slow the progression of early coronary atherosclerosis in 825 patients with angiographically documented coronary artery disease. Although there was no difference in the coronary angiographic endpoint, there was a significant reduction in the progression of carotid atherosclerosis. Moreover, although no differences were observed in the rates of all-cause mortality or major cardiovascular events, amlodipine was associated with fewer cases of unstable angina and coronary revascularization. CAMELOT (Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis)[45] was a double-blind, randomized, multicenter, 24-month trial comparing amlodipine and enalapril with placebo in 1,991 patients with angiographically documented coronary artery disease (>20% stenosis by coronary angiography) and diastolic BP < 100 mmHg. The results showed that administration of amlodipine to patients with coronary artery disease and normal BP resulted in reduced adverse cardiovascular events (HR, 0.69; 95% CI, 0.54–0.88; $P = 0.003$), although this was not the case with enalapril (HR, 0.85; 95% CI, 0.67–1.07; $P = 0.16$). Compared with baseline, intravascular ultrasound showed progression in the placebo group ($P < 0.001$), a trend toward progression in the enalapril group ($P = 0.08$), but no progression in the amlodipine group ($P = 0.31$).

Findings for Atorvastatin

The benefits of atorvastatin have been well documented, not only in the treatment of patients with CHD, but also in that of patients with hypertension or diabetes. Although the main benefits of atorvastatin come from its capacity to effectively reduce LDL-C values, different pleiotropic effects have been described.[32]

The PROVE IT-TIMI 22 trial (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators)[46] compared standard treatment (pravastatin 40 mg daily) with more intensive treatment (atorvastatin 80 mg daily) in patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days. After a mean 24-month follow-up, the median LDL-C level achieved during treatment was 95 mg/dL with pravastatin and 62 mg/dL with atorvastatin ($P < 0.001$). The hazard ratio decreased 16% in favor of atorvastatin in the primary variable of the study ($P = 0.005$), a composite endpoint of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization, and stroke. The TNT (Treating to New Targets) trial[47] studied the efficacy of low-dose versus high-dose atorvastatin in major cardiovascular events in patients with stable CHD. A total of 10,001 patients with clinically evident CHD and LDL-C levels <130 mg/dL were randomly assigned to receive either 10 mg or 80 mg of atorvastatin per day. After a follow-up of nearly 5 years, the mean LDL-C levels were 77 mg/dL with atorvastatin 80 mg and 101 mg/dL with atorvastatin 10 mg. This was reflected as an absolute risk reduction of 2.2% and a relative risk reduction of 22% (HR, 0.78; 95% CI, 0.69–0.89; $P < 0.001$) in the rate of major cardiovascular events. The ALLIANCE study (Aggressive Lipid-Lowering Initiation Abates New Cardiac Events)[48] determined whether an aggressive focused LDL-C-lowering strategy was superior to standard care for CHD patients in a real-world setting. For this purpose, a total of 2,442 CHD patients with hyperlipidemia were randomized to aggressive treatment with atorvastatin (titrated to LDL-C goals of <80 mg/dL or a maximum atorvastatin dose of 80 mg/d) or standard care (patients receiving any treatment deemed appropriate by their regular physicians) and followed for a mean of 51.5 months. Patients in the aggressive treatment arm exhibited a 17% risk reduction in the primary variable, namely, time to first cardiovascular event (HR, 0.83; 95% CI, 0.71–0.97; $P = 0.02$). Interestingly, this reduction was largely due to fewer non-fatal myocardial infarctions. More patients allocated to atorvastatin were more likely to achieve LDL-C goals (72.4% vs. 40.0%).

The REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study[49] compared the effect on burden and progression of coronary artery atheroma of regimens designed to produce intensive lipid lowering or moderate lipid lowering. Patients were randomized to receive pravastatin 40 mg/d or atorvastatin 80 mg/d for 18 months. The primary efficacy parameter was the percentage change in atheroma volume as monitored by intravascular ultrasound. LDL-C decreased from 150.2 mg/dL to 110 mg/dL in the pravastatin group and to 79 mg/dL in the atorvastatin group ($P < 0.001$). The main results of this study showed that, compared with baseline values, patients treated with atorvastatin had no change in atheroma burden, whereas patients treated with pravastatin showed progression of coronary atherosclerosis. These differences might be related to the greater reduction in atherogenic lipoproteins and C-reactive protein in patients treated with atorvastatin.

Atorvastatin has been proven to benefit not only patients with acute or chronic CHD, but also patients with diabetes or hypertension.[23,50] In ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm),[23] which involved more than 19,000 hypertensive patients (age 40–79 years, with at least three other cardiovascular risk factors) randomized to one of two antihypertensive regimens in the ASCOT trial, 10,305 patients with non-fasting total cholesterol concentrations ≤6.5 mmol/L were randomly assigned to atorvastatin 10 mg or placebo. Although the planned follow-up was five years, the study was prematurely stopped after 3.3 years, because data clearly favored those patients assigned to atorvastatin. By that time, this group showed a 36% risk reduction in the primary variable, the composite endpoint of non-fatal myocardial infarction and fatal CHD (HR, 0.64; 95% CI, 0.50–0.83; $P = 0.0005$). Fatal and non-fatal stroke, total cardiovascular events, and total coronary events were also significantly reduced by atorvastatin. CARDS (Collaborative Atorvastatin Diabetes Study)[50] assessed the effectiveness of atorvastatin 10 mg daily for primary prevention of major cardiovascular events in patients with type 2 diabetes and low LDL-C concentration. Patients were randomized to placebo or atorvastatin 10 mg daily. Once again, the trial was terminated two years earlier, with a mean follow-up of 3.9 years. The primary endpoint was time to first occurrence of acute CHD events, coronary revascularization, or stroke. Patients assigned to atorvastatin exhibited a 37% risk reduction in the primary variable (95% CI, −52 to −17; $P = 0.001$).

Findings for the Combination Amlodipine/Atorvastatin

The effects of the combination amlodipine/atorvastatin (in a single pill or in separate pills) on different outcomes have been widely reported. GEMINI (Clinical Utility of Amlodipine/Atorvastatin to Improve Concomitant Cardiovascular Risk Factors of Hypertension and Dyslipidemia)[40] was a 14-week, open-label, non-comparative, multicenter trial performed to evaluate the single-pill amlodipine/atorvastatin combination in the treatment of concomitant hypertension and dyslipidemia. Eight doses (5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40, and 10/80 mg) were electively titrated to improve BP and lipid control. A total of 1,220 patients with uncontrolled hypertension at baseline (51.9% with uncontrolled LDL-C) received the study medication. The mean dose of amlodipine and atorvastatin at the end of the trial was 7.1 mg and 26.2 mg, respectively. After 14 weeks, nearly 58% of patients achieved the BP and LDL-C goals set. These results have been confirmed in patients from diverse ethnic backgrounds.[51] CAPABLE (Clinical Utility of Caduet in Simultaneously Achieving Blood Pressure and Lipid End Points)[52] was a 20-week, open-label, non-comparative, multicenter trial to investigate the efficacy and safety of single-pill amlodipine/atorvastatin therapy for the simultaneous treatment of hypertension and dyslipidemia in African Americans. As in the GEMINI study, 8 doses of single-pill amlodipine/atorvastatin were flexibly titrated. Nearly 500 patients received therapy. At the end of the study, more than 48% of patients had achieved BP and LDL-C goals (versus 0.8% at baseline). The JEWEL program (An International, Multicentre, Open Label Study To Assess The Effectiveness Of Amlodipine - Atorvastatin Combination In Subjects With Hypertension and Dyslipidaemia) evaluated the clinical utility of the single-pill amlodipine/atorvastatin regimen in Canada and the United Kingdom (JEWEL 1) and in 11 European countries (JEWEL 2) for achieving BP and LDL-C goals.[53,54] The authors performed two 16-week, open-label studies. Patients with uncontrolled BP and controlled/uncontrolled LDL-C were treated with the single-pill combination

of amlodipine/atorvastatin. Eight doses of amlodipine/atorvastatin (5/10 mg–10/80 mg) were titrated to achieve targets. A total of 2,245 patients were included; both targets were achieved by 63% of patients in JEWEL 1 and 51% in JEWEL 2. The AVALON study[55] was a randomized, multicenter trial to determine the efficacy and safety of co-administered amlodipine and atorvastatin in patients with hypertension and dyslipidemia. The study was performed in two phases. The first phase comprised an 8-week, double-blind, placebo-controlled period during which subjects received amlodipine 5 mg, atorvastatin 10 mg, amlodipine 5 mg and atorvastatin 10 mg, or placebo. In the second phase, all individuals received single-blind amlodipine 5 mg and atorvastatin 10 mg for eight weeks, followed by 12 weeks of open-label treatment. At week eight, 45% of the patients who received amlodipine 5 mg and atorvastatin 10 mg achieved both goals. At the end of the study, about two-thirds of the patients treated with the combination (mean dose of amlodipine 7.6 mg and of atorvastatin 28.4 mg) achieved both goals. Other randomized clinical trials have shown similar results.[56,57]

Although the above data emphasize the usefulness of the combination amlodipine/atorvastatin in achieving BP and LDL-C goals, the most important study to analyze the effects of this combination was the ASCOT trial.[58] A prespecified objective of ASCOT was to assess whether there were any synergistic effects between lipid-lowering and BP-lowering regimens in preventing cardiovascular events. In ASCOT-LLA, atorvastatin reduced the relative risk of the primary endpoint of non-fatal myocardial infarction and fatal CHD events by 36% (HR, 0.64; 95% CI 0.50–0.83; $P = 0.0005$). However, when analyzing the effects of atorvastatin according to BP-lowering regimens, atorvastatin reduced the relative risk of CHD events by 53% (HR, 0.47; 95% CI, 0.32–0.69; $P < 0.0001$) in patients allocated to the amlodipine arm and by 16% (HR, 0.84; 95% CI 0.60–1.17; P = NS) in those allocated to the atenolol arm (Table 1). Importantly, differences in BP and lipid parameters (placebo-corrected) between the two antihypertensive treatment arms could not account for the differences observed in CHD outcome. These results are not surprising, given that several studies have shown that adding amlodipine to atorvastatin has anti-ischemic effects beyond lipid and BP lowering, likely due to the ability of the combination to reverse endothelial dysfunction, reduce inflammation, and improve atherosclerotic plaque.[59–64]

Table 1. Effect of atorvastatin versus placebo on primary endpoint (the combined of non-fatal myocardial infarction and fatal coronary heart disease events) in the ASCOT-LLA trial and according to the blood pressure lowering arm (ASCOT 2 × 2) (adapted from Refs. 23 and 58).

ASCOT-LLA (n = 10.305)	**ASCOT BPLA (n = 19.257) + ASCOT-LLA (n = 10.305)**
Atorvastatin vs. placebo	**ASCOT 2 × 2**
▼36% primary endpoint	**Amlodipine + atorvastatin**
(HR, 0.64; 95%	▼53% primary endpoint
CI, 0.50–0.83; $P = 0.0005$)	(HR, 0.47; 95%
	CI, 0.32–0.69; $P < 0.001$)
	Atenolol + atorvastatin
	▼16% primary endpoint
	(HR, 0.84; 95%
	CI, 0.60–1.17; $P = 0.30$)

Abbreviations: HR, hazard ratio; CI, confidence interval.

Several studies have demonstrated an additional benefit of the combination of amlodipine and atorvastatin in a single pill, namely increased adherence, which enables achievement of BP and LDL-C goals during follow-up.[65,66] Moreover, the combination of amlodipine and atorvastatin in a single pill is a cost-effective means of preventing first-onset cardiovascular disease, irrespective of the type of health care system.[67–69]

Safety of the Combination Amlodipine/Atorvastatin

The combination amlodipine/atorvastatin is safe, with a small percentage of side effects, which are mainly mild to moderate in intensity. Importantly, the combination of both drugs does not increase the likelihood of presenting adverse events when compared with each drug in monotherapy. For example, the GEMINI study[40] reported that the safety profile of the amlodipine/atorvastatin combination pill was consistent with that of its components individually. In the AVALON trial,[55] the rate of treatment discontinuation for any reason was 7.0% in patients treated with amlodipine 5 mg alone, 7.5% in patients treated with atorvastatin 10 mg alone, and 7.7% in patients treated with amlodipine 5 mg plus atorvastatin 10 mg; in other words, the rates were similar in the 3 groups, but slightly lower than

with placebo (9.6%). The most frequent side effects reported with amlodipine/atorvastatin were peripheral edema (5.3%) and myalgia (4.8%). As a result, the precautions that should be taken with the combination are the same as those that should be taken with each component alone (atorvastatin [myalgia, myopathy, elevated transaminases]; amlodipine [hypotension, peripheral edema]).

As with its individual components, the combination is contraindicated in patients with active liver disease (including unexplained persistent elevations in hepatic transaminase levels), in patients with known hypersensitivity to either component, and in pregnant women. Moreover, women taking this combination should not breastfeed their infants.

Perspective and Conclusions

The only way to reduce cardiovascular risk is to treat all risk factors and associated conditions simultaneously. Since most patients with one risk factor exhibit others, multiple regimens and combinations must be used. However, not all combinations are equally effective and safe. Physicians should use only those treatments that have been proven to be more beneficial for each patient.

The fixed combination amlodipine/atorvastatin has many advantages. On the one hand, it can effectively reduce BP and LDL-C levels with a good tolerability profile, thus leading to a greater reduction in the number of CHD events than other regimens, as the ASCOT trial showed. On the other hand, we should remember that most patients take several medications, and simplification of treatment is one way to improve adherence. In this context, fixed combinations help us to achieve this goal.

The fixed combination amlodipine/atorvastatin is indicated in patients with hypertension and hypercholesterolemia or angina.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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