REVIEW

Fixed combination of amlodipine and atorvastatin in cardiovascular risk management: patient perspectives

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Abstract: Hypertension and dyslipidemia are two of the most commonly co-occurring cardiovascular risk factors which together cause an increase in coronary heart disease-related events that is more than simply additive for anticipated event rates with each condition. Data have shown that even relatively small reductions in both blood pressure and cholesterol levels can lead to large reductions in the risk for cardiovascular events. However, though there are robust data on the beneficial effect of concomitant reduction in these risk factors, the reality is that this is achieved in <10% of patients. There is nonadherence with prescribed therapies with up to 50% of patients stopping their medications of their own volition for a variety of reasons. There is a reasonable evidence base to suggest that simplifying drug regimens and reducing pill burden will enhance patient adherence. The fixed-dose combination containing the antihypertensive agent amlodipine besylate and the statin atorvastatin is the first combination of its kind, which is both efficacious and safe and could potentially improve medication compliance, thereby improving the outcomes in these patients.

Keywords: amlodipine, atorvastatin, compliance, dyslipidemia, fixed-dose combination, hypertension

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide accounting for in excess of 930,000 deaths with an estimated direct and indirect cost of US$448.5 billion in 2008.[1] It is a multifactorial disease, emphasizing the need to treat an individuals' overall cardiovascular risk, rather than single risk factors in isolation.[2]

Hypertension and dyslipidemia are two of the most commonly co-occurring cardiovascular risk factors. In a recent study utilizing data from the third National Health and Nutrition Examination Survey (NHANES) it was estimated that almost 15% of US adults (representing approximately 30 million persons) have both hypertension and dyslipidemia.[3] It was also shown that more than 64% of patients with hypertension also have dyslipidemia; conversely, approximately 47% of patients with dyslipidemia have hypertension.[3] These two risk factors together cause an increase in coronary heart disease-related events that is more than simply additive for anticipated event rates with each disease.

Antihypertensive and lipid-lowering therapy and current practice

Antihypertensive and lipid-lowering medications substantially reduce the risk of CAD, stroke, and death in patients with cardiovascular risk factors.[4–6] Data have highlighted

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the importance of prompt and 'aggressive' control of blood pressure (BP) and cholesterol for patients with hypertension alone and for patients with additional cardiovascular risk factors including dyslipidemia and diabetes.[5,7,8] Recent trials indicate that patients with hypertension and concomitant multiple cardiovascular risk factors can benefit from lipid-lowering therapy regardless of their baseline lipid levels.[5]

Although the importance of treating hypertension and dyslipidemia is well established in treatment guidelines, the current rate of control is unsatisfactory. In a managed care population of 154,235 patients, >90% of patients in whom both hypertension and dyslipidemia had been diagnosed had not met treatment goals for both conditions.[9] Suboptimal treatment patterns exist despite national and international guidelines.[10,11] Moreover there is nonadherence with prescribed therapies; up to 50% of patients choose to stop their medications of their own volition for a variety of reasons.[12] Factors reported to influence adherence include patient education and attitudes towards treatment, cost, complexities of treatment regimen, numbers of concomitant medications, and side effects.[13,14]

There is, therefore, a reasonable evidence to suggest that simplifying drug regimens and reducing pill burden may enhance patient adherence.[13,14] A retrospective study

of patient adherence to antihypertensive and lipid-lowering therapy demonstrated improvements in adherence if both therapies were initiated simultaneously, and if fewer other medications were taken concomitantly.[13] The logic of combining multiple risk interventions for this multifactor disease is self evident and might be expected to enhance patient adherence and, therefore, improve achievement of treatment targets and reduce overall cardiovascular risk.

Combination therapy in cardiovascular disease

Polypharmacy and complex treatment regimens have been identified as important, modifiable risk factors for medication noncompliance. Poor compliance to medication regimen contributes to the practice-outcome gap, in which clinical guidelines are implemented but expected benefits are not realized. Fixed-dose combinations have the potential to improve compliance by reducing the pill burden (polypharmacy). A meta-analysis of nine studies which compared fixed-dose combinations versus free-drug components of the regimen, showed that fixed-dose combinations decreased the rate of nonadherence by 26% compared with free-drug component regimens (Figure 1).[15] A subgroup analysis of the four

Study	RR (95% CI)	% Weight
Dezii et al 2000[59]	0.74 (0.65, 0.84)	17.5
Dezii et al 2000[59]	0.71 (0.62, 0.80)	17.6
Eron et al 2000[60]	0.78 (0.55, 1.11)	4.3
Geiter et al 1987[61]	0.88 (0.55, 1.42)	2.5
Melikian et al 2002[62]	0.50 (0.35, 0.71)	4.2
Melikian et al 2002[62]	0.47 (0.22, 1.01)	1.0
NDC Dataset 2003[63]	0.81 (0.77, 0.86)	29.0
Su et al 2002[64]	0.89 (0.51, 1.57)	1.8
Taylor et al 2003[65]	0.74 (0.67, 0.81)	22.1
Overall	0.74 (0.69, 0.80)	100.0

Heterogeneity chi-squared test = 14.49 (p = 0.07)

Publication bias (Egger's) p = 0.43

−1   1   10

Risk ratio

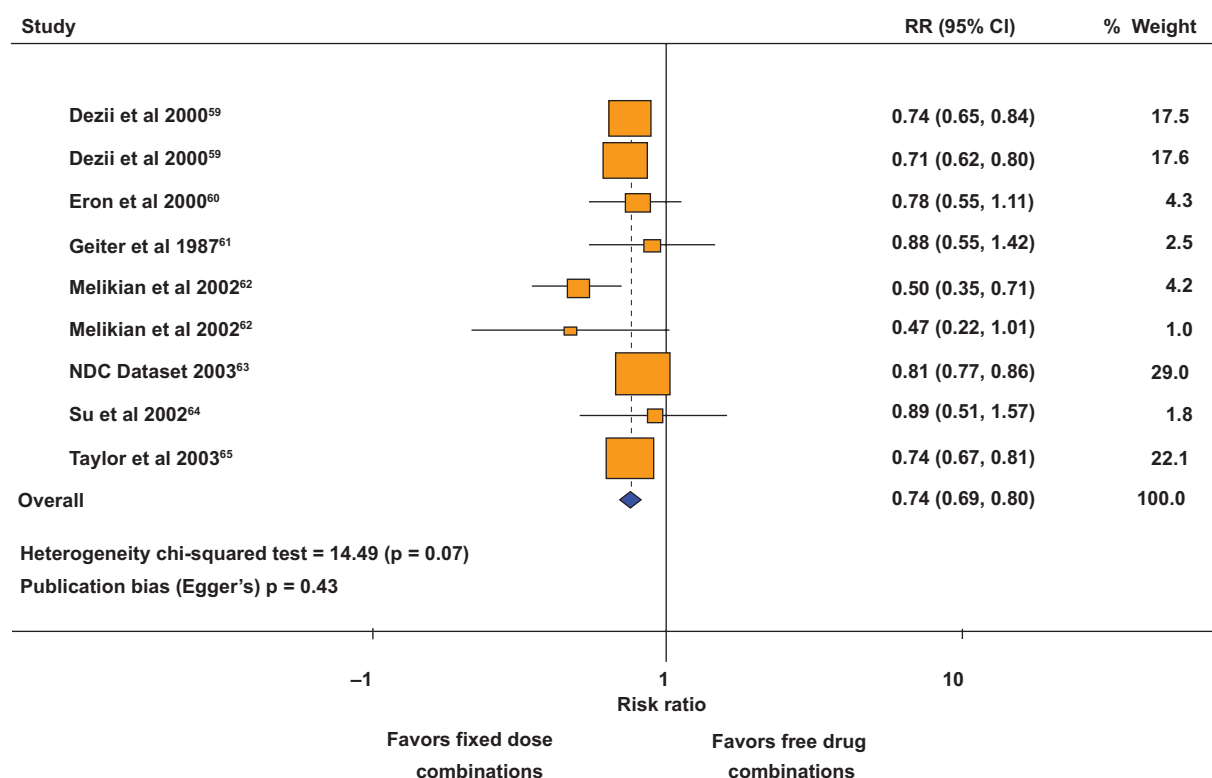Favors fixed dose combinations   Favors free drug combinations

Figure 1 Effect of fixed-dose combinations versus free-drug combination on the risk of medication nonadherence. Copyright © 2007, Elsevier. Adapted from Bangalore S, Kamalakkannan G, Parkar S, et al. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med*. 2007;120:713–719.

studies on hypertension showed that fixed-dose combination decreased the risk of medication noncompliance by 24% compared with free-drug combination regimens.[15]

The fixed-dose combination containing the antihypertensive agent amlodipine and the statin, atorvastatin, is the first combination of its kind designed to treat two risk factors for cardiovascular disease (CVD). This article provides an overview of this combination.

Overview of pharmacology of atorvastatin and amlodipine

Amlodipine component

Amlodipine besylate, a 3rd generation dihydropyridine calcium channel blocker (CCB), is approved for the treatment of hypertension and both vasospastic and chronic stable angina, alone or in combination with other agents. The primary action of amlodipine is to inhibit calcium entry through voltage-gated transmembrane L-type channels, thus decreasing intracellular calcium concentration and inducing smooth muscle relaxation.[16] Several important processes in atherosclerosis are influenced by calcium channel blockers, as they require calcium-dependent energy. Amlodipine also mediates nitric oxide release via a kinin-dependent mechanism[17] and modulates the metabolism of collagens within the extracellular matrix, and thus potentially has anti-atherosclerotic-plaque-stabilizing properties as well.[18,19] It has further been proposed that amlodipine's apparent anti-atherosclerotic properties are related to its strong lipophilicity and membrane location, allowing it to modulate the atherosclerotic process via both calcium-dependent and calcium-independent pathways.[19]

Atorvastatin component

Atorvastatin calcium is a synthetic lipid-lowering agent and is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA to mevalonate. Inhibition of HMG-CoA reductase leads to upregulation of low-density lipoprotein cholesterol (LDL-C) receptors in the liver, mediated by activation of sterol regulatory element-binding proteins resulting in enhanced clearance of LDL from the circulation and thus has an important role in preventing atherosclerosis. Atorvastatin, a second-generation statin, was introduced in 1996 and reduces LDL-C by 41%–61% in hypercholesterolemic patients.

Pharmacokinetic properties

Amlodipine/atorvastatin

The rate and extent of absorption of both amlodipine and atorvastatin after administration of a fixed-dose combination tablet has been shown to be similar to those after co-administration of matching doses of each single agent in healthy volunteers in a randomized, two-way crossover study.[20] In elderly patients, the clearance of amlodipine is reduced compared with in younger recipients, causing an increase of approximately 40%–60% in the area under the plasma concentration-time curve (AUC). As a result, a lower initial dose of amlodipine may be required in this patient group. The pharmacokinetics of amlodipine is not significantly affected in patients with renal impairment. However, in patients with hepatic impairment, clearance is reduced to a similar extent as that demonstrated in elderly patients, and a lower initial dosage may be required. In patients with moderate to severe heart failure, the increase in amlodipine AUC was similar to that observed in elderly and patients with hepatic dysfunction. Atorvastatin is associated with higher plasma concentrations in the elderly (aged 65 years) than in younger patients, with a corresponding increase in lipid-lowering efficacy. Plasma concentrations of atorvastatin are markedly increased in patients with hepatic failure and the dosage may need to be reduced.

Rationale for single-pill amlodipine/atorvastatin therapy

US epidemiological data have suggested that, on average, less than 10% of patients with concomitant hypertension and dyslipidemia are at target levels for both conditions.[9,21] The large benefits that can result from simultaneous treatment of hypertension and dyslipidemia and the current suboptimal management of these conditions demonstrate that novel solutions are needed to treat the growing number of patients who have both of these important cardiovascular risk factors. Single-pill amlodipine/atorvastatin therapy represents such a solution.

The pharmacokinetic and pharmacodynamic properties of amlodipine and atorvastatin make them well suited for combination in a single pill to manage cardiovascular risk.[22] The half-lives of both agents facilitate once-daily dosing, and both can be administered at any time of day with or without food.[23] Neither drug has any adverse effects on the other's efficacy or tolerability.[24–26]

In addition a potential synergistic and dose-dependent increase in nitric oxide release was observed with combination treatment compared with individual components in a study on human vein endothelial cells taken from healthy volunteers.[27] Moreover, combination therapy of amlodipine plus atorvastatin improved vascular compliance, an indicator of structural and functional vascular changes, and the

beneficial effect on small arteries appeared to be more than additive.[28,29] In normocholesterolemic obese hypertensive patients amlodipine plus atorvastatin reduced inflammatory markers and insulin resistance more than amlodipine therapy alone.[30] Amlodipine has demonstrated some anti-atherosclerotic properties, whereas the beneficial effects of atorvastatin on atherosclerosis, via a reduction in cholesterol levels, are more marked.[18]

Hypertension is often associated with impaired fibrinolysis, usually expressed by increased levels of plasminogen activator inhibitor type 1 (PAI-1) and decreased activity of tissue plasminogen activator (t-PA).[31] Combination therapy with amlodipine and atorvastatin improved the fibrinolytic balance more than either single agent in hypertensive hypercholesterolemic patients with insulin resistance.[31]

Study in transgenic ApoE * 3–Leiden mice demonstrates that amlodipine treatment alone did not significantly reduce atherosclerotic lesion development, whereas treatment with atorvastatin decreased lesion area substantially. The combination of amlodipine and atorvastatin tended to reduce atherosclerosis even more, possibly especially in modest statin responders, which may have implications for clinical practice.[32] Mason and colleagues have observed that the combination of atorvastatin and amlodipine produces a synergistic reduction in oxidative damage to human LDL, an effect not observed with other combinations of amlodipine and statins.[33]

The Regression Growth Evaluation Statin Study (REGRESS) trial was designed to determine the effect of lipid-lowering therapy with pravastatin in symptomatic patients with normal to moderately raised cholesterol levels. Although the REGRESS trial was not designed to evaluate combination therapy, the results suggest strongly that addition of CCBs to statin acts synergistically in retarding the progression of established coronary atherosclerosis.[34]

Key outcome trials
Amlodipine
Amlodipine effectively lowers blood pressure and reduces the risk of cardiovascular morbidity and mortality. The major outcome trials of amlodipine are listed in Table 1.

Hypertension trials
The Irbesartan Diabetic Nephropathy Trial (IDNT)[35] evaluated the effects of amlodipine or irbesartan or placebo in hypertensive patients with diabetic nephropathy. Although irbesartan was superior to amlodipine and placebo for the primary composite end point (doubling of the baseline serum creatinine concentration, the development of end-stage renal disease, or death from any cause), amlodipine reduced the time to a secondary, cardiovascular composite end point as effectively as irbesartan.[35]

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[36] more than 40,000 high risk hypertensive patients were randomly assigned to receive chlorthalidone, amlodipine, lisinopril, or doxazosin. Amlodipine was as effective as chlorthalidone in reducing the primary combined endpoint of fatal coronary heart disease or nonfatal myocardial infarction. Moreover, it was more effective than lisinopril in reducing the risk of stroke. However, incidence of heart failure was 38% higher in patients assigned to amlodipine than patients assigned to chlorthalidone.

Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial was designed to test the hypothesis that, for the same BP control, valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high cardiovascular risk.[8] Amlodipine treatment was associated with a more prompt and robust reduction in BP than valsartan treatment, particularly early in the trial. The primary composite end point of cardiac mortality and morbidity was reduced equally by both groups.[8] However, amlodipine was associated with a statistically significant 16% reduction in the incidence of myocardial infarction and a near-significant reduction in stroke (Table 1). Subanalysis of VALUE results reported that valsartan monotherapy reduced the risk of heart failure and new onset diabetes to a greater extent compared to amlodipine monotherapy.[37] These data are consistent with the findings in ALLHAT that amlodipine does not prevent heart failure as effectively as some other antihypertensive drugs.

Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA)[38] compared a "standard" antihypertensive regimen (β-blocker [atenolol] plus/minus diuretic [thiazide]) with a more "contemporary" regimen (CCB [amlodipine] plus/minus ACE inhibitor [perindopril]) on the combined primary outcome (nonfatal myocardial infarction and fatal coronary heart disease).[39] ASCOT-BPLA was terminated early due to benefits in cardiovascular mortality and all-cause mortality in patients treated with amlodipine versus atenolol-based treatment. Results from the ASCOT Conduit Artery Function Evaluation (CAFE)[40] study assessed the effects of atenolol- versus amlodipine-based therapy on central arterial blood pressure and showed that central arterial blood pressure was more favorably influenced by the amlodipine- than the atenolol-based regimen when compared with

Table 1 Key outcome studies of amlodipine

Trial	Comparison	Population	Total N	Baseline BP (mm Hg)	All-cause mortality HR (95% CI)	Myocardial infarction HR (95% CI)	Stroke HR (95% CI)
vs Placebo							
CAMELOT[43]	Placebo	Coronary artery disease	1318	129.2/77.6	1.14 (0.38–3.40)	0.73 (0.37–1.46)	0.50 (0.19–1.32)
IDNT[35]	Placebo	Hypertension and diabetic nephropathy	1136	143/79	0.90 (0.66–1.21)	NR	NR
PRAISE[41]	Placebo	Heart failure	1153		0.84 (0.69–1.02)	0.71 (0.27–1.86)	0.25 (0.03–2.27)
PREVENT[42]	Placebo	Coronary artery disease	825	129.4/78.8	0.73 (0.26–2.10)	NR	0.69 (0.51–0.93)
vs Other antihypertensive agents							
ALLHAT	Lisinopril	Hypertension	18102	146/84	0.95 (0.88–1.03)	NR	0.81 (0.71–0.93)
ALLHAT[36]	Chlorthalidone	Hypertension	24303	146/84	0.96 (0.89–1.02)	NR	0.93 (0.82–1.06)
ASCOT[38]	Atenolol	Hypertension	19257	164/94.6	0.89 (0.81–0.99)	0.87 (0.76–1.00)	0.77 (0.66–0.89)
CAMELOT[43]	Enalapril	Coronary artery disease	1336	129.2/77.4	0.92 (0.33–2.53)	1.32 (0.60–2.90)	0.76 (0.26–2.20)
FACET[58]	Fosinopril	Hypertension and diabetes	380	170/95	1.24 (0.33–4.70)	1.51 (0.56–3.06)	2.56 (0.79–8.30)
IDNT[35]	Irbesartan	Hypertension and diabetic nephropathy	1146	141/77	0.95 (0.70–1.28)	NR	NR
VALUE[8]	Valsartan	Hypertension	15245	154.6/87.5	0.96 (0.88–1.06)	0.84 (0.72–0.98)	0.87 (0.74–1.02)

Abbreviations: ALLHAT, Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BP, blood pressure; CAMELOT, Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis; FACET, Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; HR, hazard ratio; IDNT, Irbesartan in Diabetic Nephropathy Trial; PRAISE, Prospective Randomized Amlodipine Survival Evaluation; PREVENT, Prospective Randomised Evaluation of the Vascular Effects of Norvase Trial; VALUE, Valsartan Antihypertensive Long-term Use Evaluation.

peripheral BP. Central, arterial pulse pressure was observed to be a more important and an independent predictor of cardiovascular and renal outcomes.

Heart failure trials

The Prospective Randomized Amlodipine Survival Evaluation Study (PRAISE) trial[41] evaluated the safety of amlodipine in patients with severe heart failure with an ejection fraction <30%. Among patients with ischemic heart disease, there was no difference between the amlodipine and placebo groups in the occurrence of either death from any cause and hospitalization for major cardiovascular events. However, among patients with nonischemic cardiomyopathy, amlodipine reduced the combined risk of fatal and nonfatal events by 31% and decreased the risk of death by 46% and showed that it did not increase cardiovascular morbidity or mortality in patients with severe heart failure.[41]

Coronary artery disease trials

The other area of major randomized controlled trials of amlodipine have been in the cohort of patients with atherosclerosis. The Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) was a multicenter, randomized, placebo-controlled, clinical trial designed to test whether amlodipine would slow the progression of early coronary atherosclerosis in patients with angiographically documented coronary artery disease.[42] Although there was no difference in the coronary angiographic endpoint, there was a significant reduction in the progression of carotid atherosclerosis as well as a significant reduction in the risk of stroke.

Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT)[43] study compared the incidence of cardiovascular events among patients with angiographically documented coronary artery disease and normal BP randomized to amlodipine, enalapril, or placebo.[43] After 24 months, there was a significant reduction in the incidence of cardiovascular events in the amlodipine arm compared with placebo. Compared with baseline, intravascular ultrasound (IVUS) showed progression in the placebo group, a trend toward progression in the enalapril group (p = 0.08), but no progression in the amlodipine group (p = 0.31).

Atorvastatin

Atorvastatin, like other statins, has been shown to reduce LDL cholesterol and reduce the risk of cardiovascular morbidity and mortality (Table 2). In addition, statins have pleiotropic effects.

Coronary artery disease trials

The Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction (PROVE IT-TIMI 22) trial 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.[44] The primary outcome was a composite of death from any cause, myocardial infarction, severe unstable angina, revascularization or stroke. A 16% reduction in the hazard ratio favored atorvastatin. The findings from PROVE IT-TIMI 22 have been confirmed by the results from the Treating to New Targets (TNT) Study.[45]

The TNT study examined the effectiveness of low-dose versus high-dose atorvastatin therapy on major cardiovascular events. TNT demonstrated that the use of atorvastatin 80 mg to reduce LDL-C to 77 mg/dL provided additional clinical benefits in stable coronary heart disease patients, compared with reduction of LDL-C to 100 mg/dL with atorvastatin 10 mg. The composite primary outcome – first occurrence of a major cardiovascular event – showed a relative risk reduction of 22%.[46] TNT's findings confirm the growing body of evidence that reducing LDL-C below current guideline-recommended levels confers significant clinical benefits.

The Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) study compared patients with a history of acute myocardial infarction treated with a high dose of atorvastatin (80 mg/day) with those receiving the standard dose of simvastatin (20 mg/day).[47] Mean LDL-C levels were 104 mg/dL in the simvastatin group and 81 mg/dL in the atorvastatin group during treatment. The risk reduction between the treatment groups (11%) in the primary endpoint of major coronary events failed to reach significance (p = 0.07). However, significant reductions favoring the atorvastatin treatment group were observed for the occurrence of secondary cardiovascular endpoints such as coronary events and nonfatal acute myocardial infarction.

The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study used the same doses of atorvastatin and pravastatin as the PROVE IT study in patients with angiographically demonstrated CAD. The results of the REVERSAL study showed that atorvastatin 80 mg halted plaque progression (as monitored by IVUS), while pravastatin did not.[48]

The Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) trial compared a focused treatment strategy using atorvastatin with usual medical care.

Table 2 Key outcome studies of atorvastatin

Trial	Study groups	Population	Total N	All-cause mortality	Myocardial infarction	Stroke
ALLIANCE[49]	Atorvastatin (10–80 mg) vs Ongoing usual care	Coronary artery disease	2442	0.92 (0.72–1.18)	0.52 (0.38–0.74)	0.87 (0.55–1.38)
ASCOT-LLA[5]	Atorvastatin (10 mg) vs Placebo	Substudy of patients with hypertension, average or lower cholesterol, and at least three other risk factors	10305	0.87 (0.71–1.06)	0.65 (0.50–0.83)	0.73 (0.56–0.96)
CARDS[7]	Atorvastatin (10 mg) vs Placebo	Patients with diabetes without high LDL-C levels	2838	0.73 (0.53–1.01)	0.53 (0.35–0.81)	0.53 (0.31–0.90)
GREACE[50]	Atorvastatin (10–80 mg) vs usual care by GP	Heart failure	1600	0.58 (0.35–0.95)	0.46 (0.32–0.66)	0.53 (0.24–0.18)
PROVE IT[44]	Pravastatin (40 mg) vs atorvastatin (80 mg)	Acute coronary syndromes	4162	0.72 (0.5–1.02)	0.87 (0.7–1.1)	1.08 (0.4–1.6)
TNT[46]	Atorvastatin (10 mg) vs atorvastatin (80 mg)	Coronary artery disease	10001	1.01 (0.85–1.19)	0.78 (0.69–0.89)	0.75 (0.59–0.96)
IDEAL[47]	Atorvastatin (80 mg) vs simvastatin 20 mg	Coronary artery disease	8888	0.98 (0.85–1.13)	0.89 (0.78–1.01)	0.87 (0.7–1.08)

Abbreviations: ALLIANCE, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; CARDS, Collaborative Atorvastatin Diabetes Study; GREACE, Greek Atorvastatin and Coronary Heart Disease Evaluation; IDEAL, Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering; PROVE IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy trial; TNT, Treating to New Targets.

The study showed that aggressive treatment with atorvastatin was associated with significantly lower LDL cholesterol levels over usual care accompanied by improved outcomes in the composite primary end point of cardiovascular events and particularly nonfatal myocardial infarction.[49]

The Greek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study assessed the effect of atorvastatin on mortality and morbidity in patients with coronary heart disease. The treatment regimen was atorvastatin, 10–80 mg/day, titrated to LDL-C < 100 mg/dL, or usual care. Total mortality was lower with atorvastatin than with usual care. Similar reductions with atorvastatin compared to usual care were seen in coronary mortality and coronary morbidity.[50]

Hypertension and diabetes trials

In the recent Collaborative Atorvastatin Diabetes Study (CARDS), atorvastatin 10 mg reduced the death rate among patients with type 2 diabetes mellitus and relatively low-cholesterol levels by 27% compared with placebo.[7] The CARDS study was terminated after approximately two years early due to the highly significant reduction in cardiovascular events, including heart attack and stroke, in those patients receiving atorvastatin treatment.

The lipid-lowering arm of the ASCOT trial investigated, in a factorial design, the effects of simultaneous treatment with antihypertensive and lipid-lowering therapy (atorvastatin 10 mg) among hypertensive patients with normal to mildly elevated lipid levels and at least three other cardiovascular risk factors.[5] The lipid-lowering study arm was terminated nearly two years early due to the highly significant (36%) decrease in the cumulative incidence of nonfatal myocardial infarction and CHD mortality among patients receiving treatment to lower both BP and lipids compared with patients receiving treatment for hypertension alone.

Key studies evaluating amlodipine and atorvastatin combination therapy

Clinical trials have been conducted (comparative and non comparative) to assess the efficacy and safety of the combination therapy. Single-pill therapy in the Treatment of Concomitant Hypertension and Dyslipidemia (GEMINI),[22] GEMINI- Asia Pacific, Middle East, Africa, Latin America (GEMINI-ALAA),[51] An international, multicenter, open label study to assess the effectiveness of amlodipine–atorvastatin

combination in subjects with hypertension and dyslipidemia in the UK and Canada (JEWEL I), JEWEL Europe (JEWEL II),[52] Clinical Utility of Caduet in Simultaneously Achieving Blood Pressure and Lipid End Points (CAPABLE)[53] are noncomparative, titration-to-goal, multicenter studies, which showed the efficacy and effectiveness of the combination medication at achieving both LDL and BP goals. AVALON and RESPOND are two randomized double-blind, multicenter trials that compared the efficacy of the coadministration of amlodipine and atorvastatin with that of single-agent therapy or placebo over eight weeks.[25,54] The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) is a randomized, double-blind, multicenter trial that compared the efficacy of amlodipine plus atorvastatin with that of placebo over 3.3 years.[55]

ASCOT-LLA study evaluated data from patients who had received atorvastatin 10 mg once daily or placebo in addition to their antihypertensive regimen as described previously.[55] In ASCOT-LLA, the relative risk of nonfatal myocardial infarction and fatal coronary heart disease was reduced by 36% in the group receiving atorvastatin plus either antihypertensive regimen compared with the group receiving placebo plus either antihypertensive regimen.[5]

In the multicenter Atorvastatin and Amlodipine in Patients with Elevated Lipids and Hypertension (AVALON)[25] trial more patients receiving combination therapy achieved their BP goal than patients receiving atorvastatin, and more patients receiving combination therapy achieved their LDL-C goal than patients receiving amlodipine.[25] Similarly, significantly more patients receiving combination therapy achieved both their BP and LDL-C goals compared with those receiving single-agent therapy.[25] The mean Framingham estimated 10-year CHD risk was significantly with combination therapy than with single-agent therapy.

In the Efficacy and Safety of Fixed-Dose Combinations of Amlodipine and Atorvastatin in the Treatment of Patients with Concomitant Hypertension and Dyslipidemia (RESPOND)[54] study, hypertensive patients with dyslipidemia the concomitant use of amlodipine plus atorvastatin did not modify the efficacy achieved with either agent alone.[54] In an analysis of risk, the mean Framingham estimated 10-year CHD risk was reduced from mean baseline values of 15.8%–18.0% to endpoint values of 7.3%–10.7% in patients receiving combination therapy.[54]

Tolerability/safety data

In the double-blind phase of the AVALON trial, the rate of treatment discontinuation for any reason was similar in

Table 3 Noncomparative studies

Trial	Patient population	Total N	Trial period (weeks)	Baseline SBP/DBP (mmHg)	Baseline LDL-C (mg/dl)	Patients achieving both BP and LDL-C goals	Mean Framingham 10-year CHD risk score reduction
GEMINI[22]	United States. Hypertension and concurrent dyslipidemia	1220	14	146.6/87.9	152.9	57.7%	NR
GEMINI AALA[51]	27 countries in Asia, Africa, the Middle East and Latin America. Hypertension and concurrent dyslipidemia	1649	14	146.5/88.3	131.3	55.2%	51.6%
JEWEL I, II[52]	United Kingdom and Canada (JEWEL I), 11 European countries (JEWEL II). Hypertension and dyslipidemia	2245	16	152/90	193	55.5%	29%–52%.
CAPABLE[53]	African Americans. Hypertension and dyslipidemia	499	20	147.4/91.2	142.2	48.3%	50%

Abbreviations: LDL-C, low-density lipoprotein-cholesterol; CHD, coronary heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure.

groups receiving amlodipine 5 mg plus atorvastatin 10 mg (7.7%), amlodipine 5 mg alone (7.0%), or atorvastatin 10 mg alone (7.5%), but slightly higher in the placebo group (9.6%). Adverse events reported most frequently in the combination therapy group compared with the placebo group during this phase were peripheral edema (5.3% vs 2.1%), myalgia (4.8% vs 2.1%), and sinusitis (2.9% vs 0.8%).[25] In RESPOND trial combination-treated patients did not experience any increase in treatment-related side effects compared with amlodipine or atorvastatin monotherapy. The most common treatment-related side effects were peripheral edema (9.4% vs 2.7%), headache and dizziness compared to placebo. These events were mild to moderate in severity. The incidence of treatment-related myalgia in combination-treated patients was low (1.0%) and similar to that in patients treated with amlodipine alone (1.4%), atorvastatin alone (1.1%), or placebo (1.8%).[54] GEMINI study showed that amlodipine/atorvastatin combination pill has a safety profile consistent with its components. These data demonstrated that co-administered amlodipine plus atorvastatin is well tolerated in patients with hypertension and additional risk factors, and that the adverse events observed are similar in nature, severity and frequency to those seen with amlodipine or atorvastatin administered alone.

Pharmacoeconomic considerations/ quality of life

Treatment with a single tablet of amlodipine/atorvastatin has been shown to be more cost effective than two-tablet therapy and may be slightly more effective when real world adherence levels are considered.[56,57] It has been shown that the clinical and economic consequences of adding atorvastatin to an existing amlodipine-based antihypertensive regimen using a single-pill formulation versus a two-pill regimen among patients similar to the ASCOT–LLA population showed the single-pill formulation to be less costly and could be slightly more effective when real world adherence levels are considered.[57]

Conclusion

Concomitant hypertension and dyslipidemia are very common and are associated with a high risk of cardiovascular disease. Despite the widespread availability of safe and efficacious medications for the treatment of hypertension and dyslipidemia, the management of these conditions is far from optimal. Indeed, epidemiological studies have indicated that 90% of patients with concomitant hypertension and dyslipidemia fail to achieve their therapeutic targets for both

conditions. Moreover, the optimal LDL goal in patients with risk factors has been steadily declining, necessitating the treatment of bigger population subsets.

Amlodipine and atorvastatin both have excellent efficacy and safety profiles for the treatment of hypertension and dyslipidemia, respectively. Clinical trials have shown that co-administration of these two agents, across the dose range, does not modify the efficacy of either medication. Moreover, the efficacy and safety of single-pill amlodipine/atorvastatin therapy has also been demonstrated in patients at different levels of risk for CVD. The association of amlodipine and atorvastatin in a single pill formulation with flexible dosing combinations offers the possibility of simplifying the process for treating hypertension and/or angina and dyslipidemia and thereby improving medication adherence.[66] The concept of dual-therapy pill also highlights the importance of managing both the risk factors simultaneously, both for the practitioner and the patient and open the floodgates to development and release of other cross-risk-factor, single-pill combinations, and a future polypill.

Disclosure

The authors report no conflicts of interest in this work.

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