doi: 10.1111/j.1368-5031.2005.00601.x

Simultaneous treatment of hypertension and dyslipidaemia may help to reduce overall cardiovascular risk: focus on amlodipine/atorvastatin single-pill therapy

M. R. COWIE
National Heart and Lung Institute, Imperial College, London, UK

SUMMARY

Single-pill amlodipine besylate/atorvastatin calcium (Caduet®, Pfizer Inc, NY, USA) is the first therapy aimed at the simultaneous treatment of hypertension (HTN) and dyslipidaemia (DYS). The benefits of lowering blood pressure (BP) in patients with HTN and lowering cholesterol in patients with DYS are well known and well studied. However, worldwide, many patients with HTN have concomitant DYS, which places them at greater risk for cardiovascular disease compared with patients with just one of these risk factors. Clinical trials have demonstrated that amlodipine plus atorvastatin can be safely co-administered across the dose range. Single-pill amlodipine/atorvastatin reduces both BP and cholesterol and may help to improve the management of patients with concomitant HTN and DYS.

Keywords: Amlodipine; atorvastatin; hypertension; dyslipidaemia; risk factors

TREATMENT CHALLENGES IN THE MANAGEMENT OF CONCOMITANT HYPERTENSION AND DYSLIPIDAEMIA

Cardiovascular disease (CVD) is a multifactorial disease, and it is important to treat an individual's overall cardiovascular risk, rather than treating single risk factors in isolation (1). HTN and DYS are two of the most highly prevalent modifiable risk factors for CVD, and they frequently co-exist: more than 50% of patients with HTN also have DYS (Table 1) (2–9). In a recent study utilising data from the Doctors' Independent Network (DIN-LINK) database, it was estimated that 20% of adults in the UK have concomitant HTN and DYS – representing 9.2 million people (4). A similar analysis performed in the World Health Organization (WHO) MONICA (monitoring trends and determinants in CVD) project population showed that approximately 35% of western Europeans have both conditions (2). Two important studies have indicated that patients with concomitant HTN and DYS have a greater than additive risk of CVD, compared with patients who have either condition in isolation (Figure 1) (5,10).

Reductions in both blood pressure (BP) and cholesterol levels [particularly low-density lipoprotein cholesterol (LDL-C)] are central to the management of patients with concomitant HTN and DYS. Numerous studies have shown that sustained treatment of HTN and/or DYS results in reduction of cardiovascular events (11–13). Recent data have highlighted the importance of prompt and 'aggressive' control of BP and LDL-C for patients with HTN alone and for patients with additional cardiovascular risk factors including DYS and diabetes (12,14–16). For example, prompt lowering of BP has been shown to be responsible for cardiovascular event reduction among patients with HTN (14). Similarly, a regimen of intensive lipid lowering provides greater protection against death or major cardiovascular events than a standard regimen among patients with a recent acute coronary syndrome (15). Because of the greater than additive risk associated with concomitant HTN and DYS (5,10), even relatively small reductions in both BP and cholesterol levels can lead to large reductions in the risk for cardiovascular events (17,18). Furthermore, results from recent trials indicate that patients with HTN and concomitant multiple cardiovascular risk factors can benefit from lipid-lowering therapy regardless of their baseline lipid levels (12).

Guidelines recommend target levels for both HTN and DYS, with targets varying according to an individual's overall level of cardiovascular risk (19–23). However, the current level of simultaneous control of both HTN and DYS is poor, with comparatively few patients achieving recommended target levels for both conditions (7,24). Factors

Disclosure: The author provides consultancy advice to, and has received research funding from, Pfizer. He holds no stock in the company, nor has any personal or familial relationship to Pfizer employees.
Correspondence to:
Martin Cowie, MD, FRCP, Professor of Cardiology, National Heart and Lung Institute, Imperial College, Dovehouse Street, London, SW3 6LY, UK
Tel.: + 44 20 7351 8856
Email: m.cowie@imperial.ac.uk

Table 1 Estimated prevalence of concomitant hypertension and dyslipidaemia based on survey data from various populations worldwide

Population	*Number of participants*	*Prevalence of concomitant HTN/DYS*	*% of patients with HTN who also have DYS*
38 populations from 21 countries worldwide*(2)	48,000	Men: 34% (range 12–49) Women: 28% (range 14–45)	–
UK adults aged ≥16 years†(3)	9410	31%	82%
UK adults‡(4)	614,556	20%	58%
French adults aged <55 years§(5)	193,784	19%	69%
French adults aged ≥16 years¶(6)	61,108	20%	74%
US adults aged 18–80 years**(7)	7697	15%	64%
US adults with HTN††(8)			
Non-hispanic blacks	Men: 372	–	57%
	Women: 914	–	50%
Non-hispanic whites	Men: 486	–	78%
	Women: 584	–	65%

BP, blood pressure; CV, cardiovascular; CHD, coronary heart disease; DYS, dyslipidaemia; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol. Criteria for defining HTN and DYS: *HTN: BP ≥140/90 mmHg; DYS: total cholesterol ≥193 mg/dl (5.0 mM); †HTN: systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg or receiving treatment for HTN; DYS: total cholesterol concentration ≥193 mg/dl (5.0 mM) or current use of lipid-regulating therapy; ‡HTN: systolic BP >140 mmHg or diastolic BP >90 mmHg, coded entry in patient record for diagnosis of HTN, or receiving treatment for HTN; DYS: total cholesterol ≥193 mg/dl (5.0 mM), coded entry in patient record for diagnosis of DYS, or current use of lipid-regulating therapy; §HTN: systolic BP ≥140 mmHg; DYS: total cholesterol ≥200 mg/dl (5.2 mM); ¶HTN: systolic BP >140 mmHg or diastolic BP >90 mmHg or receiving treatment for HTN; DYS: total cholesterol >200 mg/dl (5.2 mM) or current use of lipid-regulating therapy; **HTN: BP ≥130/80 mmHg (patients with diabetes mellitus), ≥140/90 mmHg (patients without diabetes mellitus) or currently taking prescription medication for HTN; DYS: LDL-C >100 mg/dl (2.6 mM) if CHD, ≥130 mg/dl (3.4 mM) if ≥ two CV risk factors, ≥160 mg/dl (4.1 mM) if < two CV risk factors or current use of lipid-regulating therapy; ††HTN: prior diagnosis of HTN and current use of prescription antihypertensive medications or BP >140/90 mmHg; DYS: LDL-C >100 mg/dl (2.6 mM) if CHD, ≥130 mg/dl (3.4 mM) if ≥ two CV risk factors, ≥160 mg/dl (4.1 mM) if < two CV risk factors or HDL-C <35 mg/dl (0.9 mM) or triglycerides ≥200 mg/dl (2.3 mM) or current use of lipid-regulating therapy.

contributing to inadequate goal attainment include poor screening rates for DYS, the low number of patients diagnosed with concomitant HTN and DYS who are receiving treatment for both conditions (2,4) and poor adherence – by physicians to treatment guidelines and by patients to their prescribed medications (25).

PHARMACOLOGIC TREATMENT OF HYPERTENSION AND DYSLIPIDAEMIA

A number of different classes of therapy are available for the initial treatment of HTN including diuretics, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs) and angiotensin receptor blockers (ARBs) (13). Recent guidelines for the management of HTN recommend a step-wise approach, with the use of multiple antihypertensive therapies being necessary for many patients with HTN (19–21). For DYS, statins are universally accepted as the first-line drug treatment (22,23).

A single-pill therapy combining amlodipine and atorvastatin at 11 different dosage strengths has recently been approved in the USA for the simultaneous treatment of HTN and DYS. Single-pill co-treatment of two cardiovascular risk factors simplifies the treatment regimen and has the potential to improve the management of patients with concomitant HTN and DYS. Amlodipine is a dihydropyridine CCB which has been demonstrated to be an effective and well-tolerated treatment for HTN and/or angina (14,26,27). Similarly, an extensive clinical trial programme has shown the statin, atorvastatin, to be an effective and well-tolerated treatment for DYS (12,15,16,28).

In this review, the profile of this first single-pill therapy aimed at the simultaneous treatment of HTN and DYS will be discussed.

USE OF AMLODIPINE AND ATORVASTATIN IN THE TREATMENT OF PATIENTS AT RISK FOR CVD

The results of a number of recent clinical studies have highlighted the benefits of the treatment of HTN and DYS in patients at high risk of CVD. These studies have also demonstrated that amlodipine and atorvastatin can play an important role in the treatment of HTN and DYS, respectively.

Amlodipine

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial (14) was designed to test the hypothesis that, for

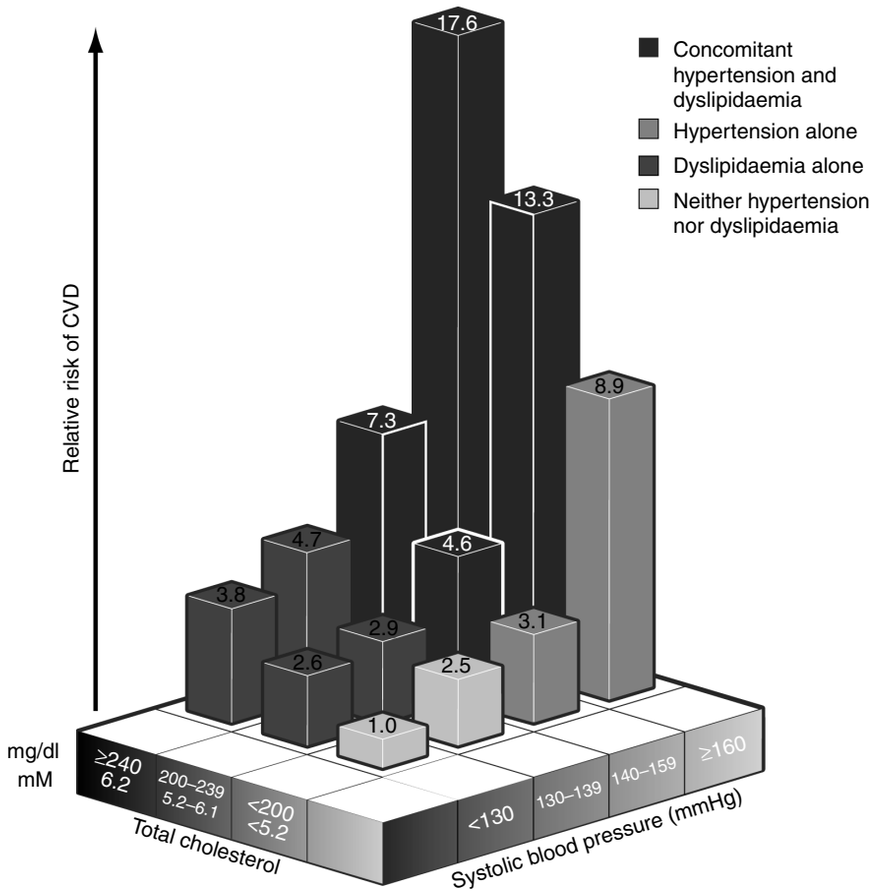

Figure 1 Relationship between relative risk of cardiovascular disease (CVD) and rising cholesterol and systolic blood pressure levels among 108,879 French men aged <55 years (derived from Thomas et al. 2002) (5). Patients with systolic BP ≥140 mmHg and total cholesterol ≥200 mg/dl were classified as having hypertension and dyslipidaemia, respectively

the same BP control, valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high cardiovascular risk. BP was reduced by both treatments, but the effects of the amlodipine-based regimen were more pronounced, especially in the early period (BP 4.0/2.1 mmHg lower in the amlodipine than the valsartan group after 1 month; 2.1/1.6 mmHg lower after 6 months; $p < 0.001$ between groups for both). At study end (72 months), BP reduction from baseline was 17.3/9.9 mmHg for the amlodipine group and 15.2/8.2 mmHg for the valsartan group ($p < 0.0001$). The primary composite end point of cardiac mortality and morbidity occurred in 10.6% of patients in the valsartan group (25.5 per 1000 patient-years) and in 10.4% of patients in the amlodipine group (24.7 per 1000 patient-years; hazard ratio 1.04; 95% confidence interval, 0.94–1.15, $p = 0.49$). Furthermore, amlodipine was associated with a statistically significant 19% reduction in the incidence of myocardial infarction and a near-significant ($p = 0.08$) 15% reduction in stroke.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (29) demonstrated that there were no differences in the incidence of coronary heart disease (CHD) mortality or nonfatal myocardial infarction between an amlodipine-based regimen and a diuretic- or ACE inhibitor-based regimen. The findings of VALUE and ALLHAT emphasise the benefits of prompt, aggressive BP control in hypertensive patients at high cardiovascular risk and that amlodipine, used alone or in combination with other BP-lowering agents, is suitable for achieving this objective.

The recently reported Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared the incidence of cardiovascular events among 1991 patients with angiographically documented coronary artery disease and normal BP (mean BP at baseline, 129/78 mmHg) randomised to amlodipine 10 mg, enalapril 20 mg or placebo (30). After 24 months, there was a significant reduction in the incidence of cardiovascular events in the amlodipine arm compared with placebo (hazard ratio, 0.69; 95% CI, 0.54–0.88; $p = 0.003$). Directionally similar but smaller and statistically nonsignificant treatment effects were observed with enalapril. A substudy of 274 CAMELOT participants measured atherosclerosis progression by intravascular ultrasound (IVUS). Compared with baseline, IVUS showed progression in the placebo group ($p < 0.001$), a trend toward progression in the enalapril group ($p = 0.08$), and the absence of progression in the amlodipine group ($p = 0.31$).

Amlodipine has no known clinically relevant drug–drug interactions with other BP-lowering agents, an important property, given the guideline recommendations to use more than one antihypertensive medication in the treatment of patients with HTN in order to effectively lower BP to recommended target levels (19–21). This property of amlodipine is

particularly relevant for older patients who are likely to be taking medication for other diseases in addition to HTN (31).

Atorvastatin

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial (15) compared standard treatment (pravastatin 40 mg daily) with more intensive treatment (atorvastatin 80 mg daily) in patients who had been hospitalised for an acute coronary syndrome within the preceding 10 days. The primary outcome was a composite of the interval between randomisation and death from any cause, myocardial infarction, severe unstable angina, revascularisation or stroke. After 30 days, the median LDL-C in patients who had not previously received statin treatment declined by 22% and 51% in the pravastatin and atorvastatin groups, respectively. Rates of the primary end point at 2 years were 26% in the pravastatin group and 22% with high-dose atorvastatin therapy. A 16% reduction in the hazard ratio favoured atorvastatin ($p = 0.005$). The benefit gained from high-dose therapy was evident by 30 days and persisted over time. The findings from PROVE IT-TIMI 22 have been confirmed by the results from the Treating to New Targets Study (32), which demonstrated that intensive lipid-lowering therapy with 80 mg of atorvastatin per day in patients with stable CHD provided significant clinical benefit beyond that afforded by less aggressive treatment with 10 mg of atorvastatin per day.

The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study (33) used the same doses of atorvastatin and pravastatin as the PROVE IT study in patients with angiographically demonstrated CHD. The results of the REVERSAL study showed that atorvastatin 80 mg halted plaque progression (as monitored by IVUS), while pravastatin did not. In the recent Collaborative Atorvastatin Diabetes Study (CARDS) (16), atorvastatin 10 mg reduced the death rate among patients with type 2 diabetes mellitus and relatively low-cholesterol levels (LDL-C$\leq$4.14 mM) by 27% compared with placebo ($p = 0.059$). The CARDS study was terminated approximately 2 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 Anglo-Scandinavian Cardiac Outcomes Trial (12) 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. The lipid-lowering study 'arm' was terminated nearly 2 years earlier than expected 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 HTN alone (Figure 2).

RATIONALE FOR SINGLE-PILL AMLODIPINE/ ATORVASTATIN THERAPY

It is clear that the treatment of HTN and DYS reduces the incidence of CVD and that patients with concomitant HTN and DYS are at greater risk of CVD compared with those with only one of these cardiovascular risk factors. A study of 108,879 French men aged 18–55 years showed that a combination of elevated BP and elevated serum cholesterol increases an individual's risk for CVD compared with the risk associated with elevations in only one of these parameters (5). The simultaneous treatment of both risk factors has the potential to greatly reduce the incidence of CVD among these high-risk patients. Indeed, one recent evaluation of strategies aimed at primary prevention of CVD has indicated that pharmacologic treatment of both HTN and DYS – resulting in 10% reductions in mean blood cholesterol and BP – could reduce the incidence of major CVD by 45% (17).

Current management of HTN and/or DYS is less than optimal: observational data indicate that screening, diagnosis and treatment rates are low (2,34,35). The majority of patients diagnosed with concomitant HTN and DYS are not receiving treatment for both risk factors (2,4,7). In an analysis of UK adults in 2003–04, Williams and colleagues (4) reported that 75% of 122,962 patients with concomitant HTN and DYS were not receiving treatment for both conditions (Figure 3). In this study, even among patients who were receiving both antihypertensive and lipid-lowering therapy, only 42% were at UK-recommended goals for both BP and total cholesterol (4). Furthermore, US epidemiological data have suggested that, on average, less than

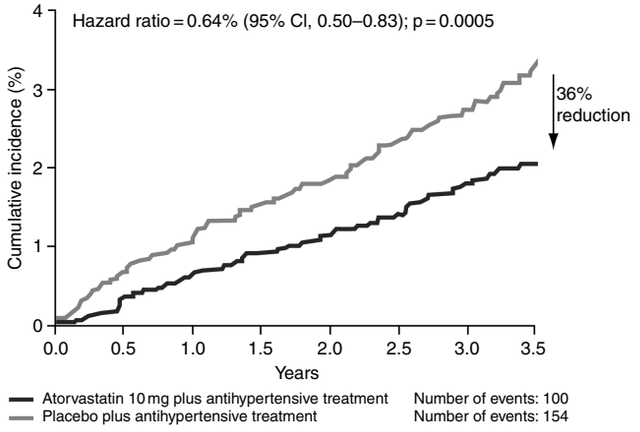

Figure 2 Cumulative incidence of nonfatal myocardial infarction and fatal coronary heart disease in the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (12). All patients ($n = 10,305$) received antihypertensive treatment, and 5168 patients were randomised to atorvastatin 10 mg. Reprinted with permission from Elsevier (*The Lancet* 2003; 361: 1149–1158) (12)

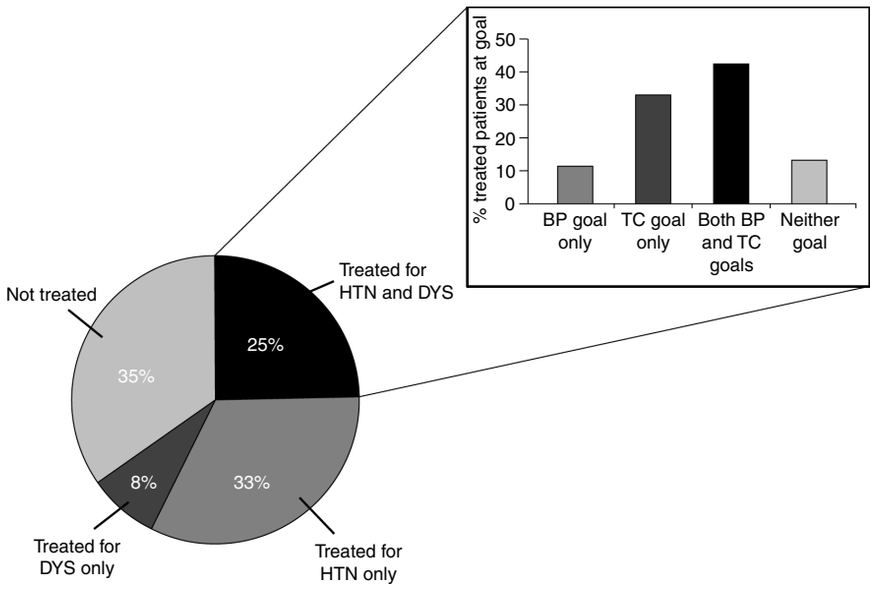

Figure 3 The pie chart illustrates the percentage of UK patients with concomitant hypertension (HTN) and dyslipidaemia (DYS) ($n = 122{,}962$) receiving treatment for one, both or neither condition in 2003–2004. The bar chart shows attainment of blood pressure (BP), total cholesterol (TC), 'both' and 'neither' goals among the patients who were receiving treatment for both conditions (derived from Williams et al. 2004) (4)

10% of patients with concomitant HTN and DYS are at goal for both conditions (7,24).

The large benefits that can result from simultaneous treatment of HTN and DYS 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, combining two well-tolerated once-daily agents, which have proven to be highly efficacious in lowering BP and LDL-C, respectively. No drug–drug interactions have been reported between amlodipine and atorvastatin, and both can be taken at any time of day with or without food with no adverse effect on efficacy. Additionally, the amlodipine/atorvastatin single pill has been demonstrated to be bioequivalent to its components (36).

CLINICAL STUDIES INVESTIGATING SIMULTANEOUSLY ADMINISTERED AMLODIPINE AND ATORVASTATIN

Three recent studies have evaluated the use of simultaneously administrated amlodipine and atorvastatin in the treatment of patients with concomitant HTN and DYS: the Avalon study, the Respond study and the Gemini study (37–40). The Avalon and Respond studies investigated amlodipine plus atorvastatin co-administered as separate tablets; the Gemini study determined the clinical utility of single-pill amlodipine/atorvastatin.

The initial phase of the Avalon study was an 8-week, multicentre, randomised, double-blind, placebo-controlled trial designed to determine whether once-daily co-administration of amlodipine 5 mg plus atorvastatin 10 mg was superior to amlodipine 5 mg plus placebo in the treatment of DYS and atorvastatin 10 mg plus placebo in the treatment of HTN (37). A total of 847 patients participated in the study. Patients receiving combination amlodipine plus atorvastatin therapy were significantly more likely to attain recommended goals for both systolic BP and LDL-C (46% patients attained their recommended target levels for both conditions) compared with patients receiving either monotherapy or placebo (38). There was no modification of efficacy associated with co-administration of amlodipine 5 mg and atorvastatin 10 mg.

The Respond study was an 8-week, multinational, multicentre, randomised, double-blind, placebo-controlled, 3×5 factorial study designed to assess the safety and efficacy of amlodipine and atorvastatin co-administered as separate tablets on LDL-C and systolic BP levels vs. either drug alone (39). The objective of the study was to establish whether amlodipine modifies the lipid-lowering efficacy of atorvastatin and whether atorvastatin modifies the BP-lowering efficacy of amlodipine. The co-primary efficacy parameters were the change from baseline to end point in LDL-C and systolic BP. A total of 1660 patients with concomitant HTN and DYS were randomised to receive amlodipine (5 or 10 mg), atorvastatin (10, 20, 40 or 80 mg), eight combinations of these amlodipine plus atorvastatin doses or placebo. Almost all (96.9%) of the participants had at least one cardiovascular risk factor in addition to HTN and DYS. All eight amlodipine plus atorvastatin dose combinations reduced LDL-C significantly more than amlodipine monotherapy (range: 36.6–49.1%; all $p < 0.001$) and reduced systolic BP significantly more than atorvastatin monotherapy (range: 12.2–17.6 mmHg; all $p < 0.001$). There was no modification of efficacy associated with co-administration of amlodipine and atorvastatin. The most common treatment-related adverse events (AEs) (pooled across the dose range)

occurring in patients treated with amlodipine plus atorvastatin were peripheral oedema, headache and respiratory tract infection; these events were mild to moderate in severity. Combination-treated patients did not experience any increase in AEs compared with either amlodipine or atorvastatin monotherapy. It was concluded that a fixed-dose combination of amlodipine plus atorvastatin across the dose range for both drugs is a safe, effective means of treating concomitant HTN and DYS in a broad range of patients at differing levels of risk for CVD.

The Gemini study was a 14-week, open-label, noncomparative, multicentre trial designed to investigate the clinical utility of single-pill amlodipine/atorvastatin therapy in patients with concomitant HTN and DYS in a real-world setting (40). The primary efficacy parameter was the percentage of patients achieving both BP and LDL-C treatment goals at end point. Eight dosage strengths of amlodipine/atorvastatin single pill (5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40 and 10/80 mg) were electively titrated by the investigators to improve BP and lipid control. Amlodipine/atorvastatin was either added into the existing hypertensive treatment regimen, initiated as first-line therapy, or patients already taking either amlodipine or atorvastatin were switched to the single-pill therapy. Investigators could select the starting dose of amlodipine/atorvastatin single-pill on the basis of the individual patient's level of cardiovascular risk and their previous treatment regimen for HTN and DYS. A total of 1220 patients were enrolled in the study most of whom (more than 85%) had cardiovascular risk factors in addition to HTN and DYS. Nearly 50% of study participants had not been receiving treatment for both their HTN and DYS prior to study entry. The mean dose of study drug administered at the end of the study period was amlodipine 7.1 mg/atorvastatin 26.2 mg. Overall, 58% of patients achieved goal for both conditions at end point. Dual goal attainment was highest among patients with additional risk factors, but without CHD or CHD equivalents: 76% of these patients achieved both goals at study end. Fifty-eight patients (4.8%) discontinued due to AEs. The most common AEs were respiratory tract infection (11.9%), peripheral oedema (8.8%), headache (5.4%) and myalgia (4.2%). The safety profile for single-pill amlodipine/atorvastatin was consistent with both amlodipine and atorvastatin alone. It was concluded that amlodipine/atorvastatin single-pill therapy is an effective and well-tolerated treatment for all patients with concomitant HTN and DYS, regardless of their level of cardiovascular risk and whether administered as initial or add-on therapy over a variety of dosing regimens.

Post hoc analyses of the Gemini study have demonstrated the utility of single-pill amlodipine/atorvastatin across a broad range of high-risk patient populations: African Americans, the elderly, patients with CHD and patients with type 2 diabetes mellitus (41,42). The ongoing CAPABLE (Clinical utility of Caduet in simultaneously Achieving Blood Pressure and Lipid Endpoints) trial has been designed to further investigate the clinical utility of single-pill amlodipine/atorvastatin therapy among African Americans who have concomitant HTN and DYS; in this trial, amlodipine/atorvastatin single pill can be taken as first-line therapy, as switch therapy for patients previously taking amlodipine alone or atorvastatin alone or in addition to the patient's existing, non-CCB antihypertensive treatment regimen (43). The results of this study are particularly eagerly anticipated, as CVD tends to occur earlier and is associated with a higher mortality among African Americans than among whites of a similar age (44). It is worth noting that multiple antihypertensive agents are often needed to control BP. In accordance with the 'AB/CD rule' (45), an ACE inhibitor or ARB might be recommended as first-line antihypertensive therapy for certain patient populations, for example for young Caucasians due to their high renin status. However, such patients will often require more than one agent to achieve recommended targets; therefore, a CCB can also be prescribed as part of the treatment regimen (46). Indeed, it has been demonstrated that amlodipine can be effectively administered with beta-blockers, thiazide diuretics, ACE inhibitors and ARBs and provides incremental reductions in BP (47). Finally, while it may be argued that certain other combinations of antihypertensive plus statin therapy may be more suited for particular patient types, amlodipine/atorvastatin single-pill therapy combines two of the most commonly prescribed, safe and effective treatments for reducing BP and lipids. It will be interesting to see which other antihypertensive/lipid-lowering combination drugs are developed in the future.

CONCLUSION

Concomitant HTN and DYS are very common and are associated with a high risk of CVD. Despite the widespread availability of safe and efficacious medications for the treatment of HTN and DYS, the management of these conditions is far from optimal. Indeed, epidemiological studies have indicated that 90% of patients with concomitant HTN and DYS fail to achieve their therapeutic targets for both conditions. Amlodipine and atorvastatin both have excellent efficacy and safety profiles for the treatment of HTN and DYS, respectively. Recent studies have highlighted the benefits of the prompt treatment of HTN and DYS using these medications. 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 combination amlodipine/atorvastatin pill is a new approach to treatment, which should help to improve the management of total cardiovascular risk in patients with

concomitant HTN and DYS and thereby reduce the incidence of CVD in this large patient population.

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Paper received February 2005, accepted May 2005