Improved Attainment of Blood Pressure and Cholesterol Goals Using Single-Pill Amlodipine/Atorvastatin in African Americans: The CAPABLE Trial

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OBJECTIVE: **To investigate the efficacy and safety of single-pill amlodipine/atorvastatin therapy for the simultaneous treatment of hypertension (HTN) and dyslipidemia in African Americans.**

PATIENTS AND METHODS: **Conducted between July 19, 2004, and August 9, 2005, the Clinical Utility of Caduet in Simultaneously Achieving Blood Pressure and Lipid End Points trial was a 20-week, open-label, noncomparative, multicenter trial of the efficacy and safety of single-pill amlodipine/atorvastatin in controlling elevated blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) in African Americans with concomitant HTN and dyslipidemia and either no additional risk factors, 1 or more cardiovascular risk factors, or coronary heart disease or a risk equivalent. Eight dosage strengths of single-pill amlodipine/atorvastatin were flexibly titrated. The primary efficacy assessment of the main trial was the percentage of patients who attained the LDL-C treatment goals of both the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the National Cholesterol Education Program Adult Treatment Panel III.**

RESULTS: **Of the 1170 African American patients screened, 501 were enrolled in the study and 499 received drug therapy. At end point, 236 (48.3%) of 489 patients reached both their BP and LDL-C goals (vs 4 [0.8%] of 484 at baseline); 280 (56.8%) of 493 reached BP goals (vs 7 [1.4%] of 494 at baseline); and 361 (73.7%) of 490 reached LDL-C goals (vs 138 [28.5%] of 484 at baseline). Among the 499 patients receiving drug therapy, common treatment-related adverse events were peripheral edema (17 patients [3.4%]), headache (11 [2.2%]), myalgia (11 [2.2%]), and constipation (10 [2.0%]).**

CONCLUSION: **Single-pill amlodipine/atorvastatin therapy was well tolerated and effectively targeted HTN and dyslipidemia in this population of African Americans who were at risk of cardiovascular disease.**

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AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; CAPABLE = Clinical Utility of Caduet in Simultaneously Achieving Blood Pressure and Lipid End Points; CK = creatine kinase; CV = cardiovascular; GGT = γ-glutamyl transpeptidase; HTN = hypertension; ITT = intention-to-treat; JNC 7 = Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL-C = low-density lipoprotein cholesterol; SAE = serious AE; SBP = systolic BP; ULN = upper limit of normal

African Americans have among the highest overall mortality due to coronary heart disease of any racial/ethnic group in the United States. Compared with whites, African Americans have a 2-fold greater risk of stroke[1,2] and a higher prevalence of hypertension (HTN).[1,3] Approximately 80% of patients with HTN have additional cardiovascular (CV) risk factors, such as dyslipidemia, which further increase their risk of CV events.[4] According to the 2001-2002 National Health and Nutrition Examination Survey (NHANES), the prevalence of concomitant HTN and dyslipidemia in African Americans was higher (21.7%) than in the overall NHANES population (18.3%).[3] Antihypertensive and lipid-lowering therapies have been shown to reduce CV events in a broad range of patients.[5-10] The importance of a multifactorial approach including both antihypertensive and lipid-lowering therapy has become increasingly apparent.[8,11,12] However, few patients are adequately treated. For example, only 6.5% of African Americans with concomitant HTN and dyslipidemia attain their blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) goals vs 9.0% of the overall US population.[3]

Poor adherence to antihypertensive and lipid-lowering therapies plays an important role in this poor control.[13,14] Adherence is adversely affected by increasing pill burden.[13] Therefore, combination pills containing both antihypertensive and lipid-lowering agents could improve the management of CV risk. Indeed, recent results suggest that

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patients receiving a single pill containing amlodipine/atorvastatin are 2 to 3 times more likely to be adherent than those receiving either coadministered amlodipine and atorvastatin or other 2-pill combinations of calcium channel blockers and statins.[14]

Two placebo-controlled trials have shown that the coadministration of amlodipine and atorvastatin is an effective and well-tolerated therapy for HTN and dyslipidemia in patients with and without coronary heart disease.[15,16] The open-label Gemini trial obtained similar results with the same drug combination in a single pill.[17,18] Post hoc analysis of the Gemini study demonstrated effective BP and LDL-C level reduction in the relatively small population of African American patients who were not at goal for either HTN or dyslipidemia at baseline.[18] This group warrants further study because previous trials have shown that African Americans have LDL-C responses to statins that are 3% to 6% lower than those seen in the white population.[19,20] Furthermore, African Americans have generally been underrepresented in clinical trials of statins.[21] The Clinical Utility of Caduet in Simultaneously Achieving Blood Pressure and Lipid End Points (CAPABLE) trial investigates the efficacy, safety, and clinical utility of single-pill amlodipine/atorvastatin therapy for the simultaneous treatment of HTN and dyslipidemia in African Americans, as initial treatment or in combination with other antihypertensive drugs.

PATIENTS AND METHODS

Study Population

Self-identified African American men and women (18-80 years) with uncontrolled HTN (treated or untreated) and dyslipidemia (treated or untreated) were recruited. Patients were excluded if their BP was at goal or if they were receiving both amlodipine and atorvastatin, 10 mg of amlodipine (or other maximum-dose calcium channel blocker), or 80 mg of atorvastatin (with LDL-C levels of 100 mg/dL or greater [to convert to millimoles per liter, multiply by 0.0259]). Additional exclusion criteria included pregnancy/lactation; impaired renal or hepatic function; myocardial infarction within 6 months of screening; coronary revascularization, atherosclerotic stroke, or transient ischemic attack within 3 months of screening; history of cardiomyopathy or chronic heart failure; secondary HTN; or secondary dyslipidemia.

Study Design

The CAPABLE trial was a 20-week, office-based, open-label, noncomparative, multicenter trial that was conducted between July 19, 2004, and August 9, 2005. To approximate "real-world" practice in a clinical trial setting and to provide information on the likely utilization of the single pill in the clinic, previously treated or treatment-naïve patients with HTN and dyslipidemia and with and without additional CV risk factors (eg, diabetes, coronary heart disease) were recruited. Although BP and LDL-C goals were prespecified, investigators could select and titrate study medication doses, each component independently of the other, as they would in clinical practice.

Patients were assigned to 3 CV risk groups based on criteria outlined in the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[22] and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[23] guidelines (Table 1). For CV risk group 3, the BP treatment goal was less than 130/80 mm Hg, as recommended for patients with diabetes mellitus.[22]

Eight different dosages of single-pill amlodipine/atorvastatin therapy were administered: 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40, and 10/80 mg. The amlodipine component of the single pill was prescribed as: (1) initial antihypertensive therapy (patients untreated for HTN), (2) substitution therapy (for patients taking amlodipine), (3) switch therapy (for patients taking other calcium channel blockers), or (4) adjunctive therapy (for patients following a non–calcium channel blocker antihypertensive regimen). The atorvastatin component of the single pill was taken as: (1) initial lipid-lowering therapy (for patients untreated for dyslipidemia), (2) substitution therapy (for patients receiving atorvastatin), or (3) switch therapy (for patients taking other lipid-lowering medication). All lipid-regulating drugs were discontinued at entry, with the exception of the study drug or ezetimibe, if previously administered. Prior BP medication, other than calcium channel blockers, could be continued.

Blood pressure and lipid levels were measured at screening, at enrollment, and at weeks 4, 6, 10, 14, and 20. The mean of 3 seated BP readings was calculated. Upward and downward titration of either the amlodipine or atorvastatin component could occur at weeks 4 (amlodipine only), 6, 10, and 14 at the discretion of the investigator. At each visit, patients were reminded to adhere to dietary guidelines if their BP or LDL-C levels were not at goal.[24] Patients who missed titration visits were not discontinued from the study.

The study was conducted in accordance with good clinical practice, including the International Conference on Harmonization Guidelines and the most recent version of the Declaration of Helsinki. The trial protocol was approved by each center's institutional review board and all patients gave informed consent to participate.

Efficacy Measures

The primary efficacy parameter was the percentage of intention-to-treat (ITT) patients who reached both their JNC

TABLE 1. **Cardiovascular Risk Categories and Corresponding BP and LDL-C Target Levels in the CAPABLE Trial**[a]

	Group 1 (n=90)	Group 2 (n=164)	Group 3 (n=245)
Cardiovascular risk factors for CHD	HTN and dyslipidemia with no ARF	HTN and dyslipidemia with ≥1 ARF, excluding CHD and DM	HTN and dyslipidemia with CHD or CHD risk equivalent (DM or other atherosclerotic disease)
Entry criteria			
SBP (mm Hg) and/or	140-179	140-179	130-159
DBP (mm Hg)	90-109	90-109	85-99
LDL-C (mg/dL), drug-naïve[b]	160-250	130-250	100-250
LDL-C (mg/dL), treated[b,c]	≤170	≤170	≤170
Treatment goals			
JNC 7[22]			
BP goal (mm Hg)	<140/90	<40/90	<130/80[d]
NCEP ATP III[23]			
LDL-C goal (mg/dL)[b]	<160	<130	<100

[a] ARF = additional risk factor; BP = blood pressure; CAPABLE = Clinical Utility of Caduet in Simultaneously Achieving Blood Pressure and Lipid End Points; CHD = coronary heart disease; DBP = diastolic BP; DM = diabetes mellitus; HTN = hypertension; JNC 7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL-C = low-density lipoprotein cholesterol; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; SBP = systolic BP.
[b] SI conversion factor: To convert LDL-C value to millimoles per liter, multiply by 0.0259.
[c] Treated with lipid-lowering medication.
[d] For patients in Group 3, the CAPABLE trial used the more conservative treatment goals that are usually reserved for patients with DM.

7 BP and NCEP ATP III LDL-C goals at end point (week 20 or, for patients who discontinued prematurely, the final visit). Secondary efficacy parameters included changes from baseline in systolic BP (SBP), diastolic BP, LDL-C, and other lipid parameters.

Safety Assessments

For the safety analysis, treatment-related adverse events (AEs) in patients who took at least 1 dose of study medication and had any follow-up safety assessment were summarized descriptively.

Clinical Laboratory Test Abnormalities

To determine clinical laboratory test abnormalities in muscle and hepatic enzyme levels, serum chemistry screens of creatine kinase (CK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), alkaline phosphatase, and total bilirubin were performed at screening, at randomization/enrollment, and at weeks 6, 10, 14, and 20 (or at early termination).

Levels of CK greater than 5 times the upper limit of normal (ULN) or greater than 10 times the ULN were recorded. The normal range of CK was defined as 18 to 198 U/L for men and 18 to 169 U/L for women. Patients with a CK level of 10 times the ULN or higher were discontinued from the trial, and follow-up measurements of CK were continued until the abnormality resolved.

Elevations in liver function tests of greater than 3 times the ULN were also captured. Normal ranges were as follows: ALT, 6 to 34 U/L (to convert to microkatals per liter, multiply by 0.0167); AST, 9 to 34 U/L (to convert to microkatals per liter, multiply by 0.0167); GGT, 4 to 49 U/L (to convert to microkatals per liter, multiply by 0.0167); alkaline phosphatase, 35 to 123 U/L (to convert to microkatals per liter, multiply by 0.0167); and total bilirubin, 0.2 to 1.2 mg/dL (to convert to micromoles per liter, multiply by 17.104). Patients with ALT or AST levels 3 times the ULN (confirmed by a second measurement within 7 days) were withdrawn from the trial.

Statistical Analyses

For this noncomparative open-label study, approximately 500 patients at 100 sites were to be enrolled. This sample size was not based on power calculations: rather, it was selected to give a reasonable likelihood of observing therapeutic effects and AEs across a broad spectrum of clinical circumstances, including 3 CV risk groups and 8 available dosage combinations. Efficacy parameters were evaluated at baseline and end point and were summarized for all ITT patients (patients who took at least 1 dose of study medication and had any postenrollment efficacy data), all ITT patients with uncontrolled LDL-C at baseline, and each CV risk group (1, 2, and 3). The numbers, percentages, and 95% confidence intervals for the proportion of patients reaching their BP and/or LDL-C goals were calculated at end point. Data were analyzed using Statistical Analysis Software (SAS; SAS Institute, Cary, NC).

RESULTS

Patient Demographics and BP and LDL-C Levels at Baseline

Of the 1170 African American patients screened, 501 were enrolled and 499 received study medication. Of these, 374 patients (74.9%) completed the study and 125 (25%) dis-

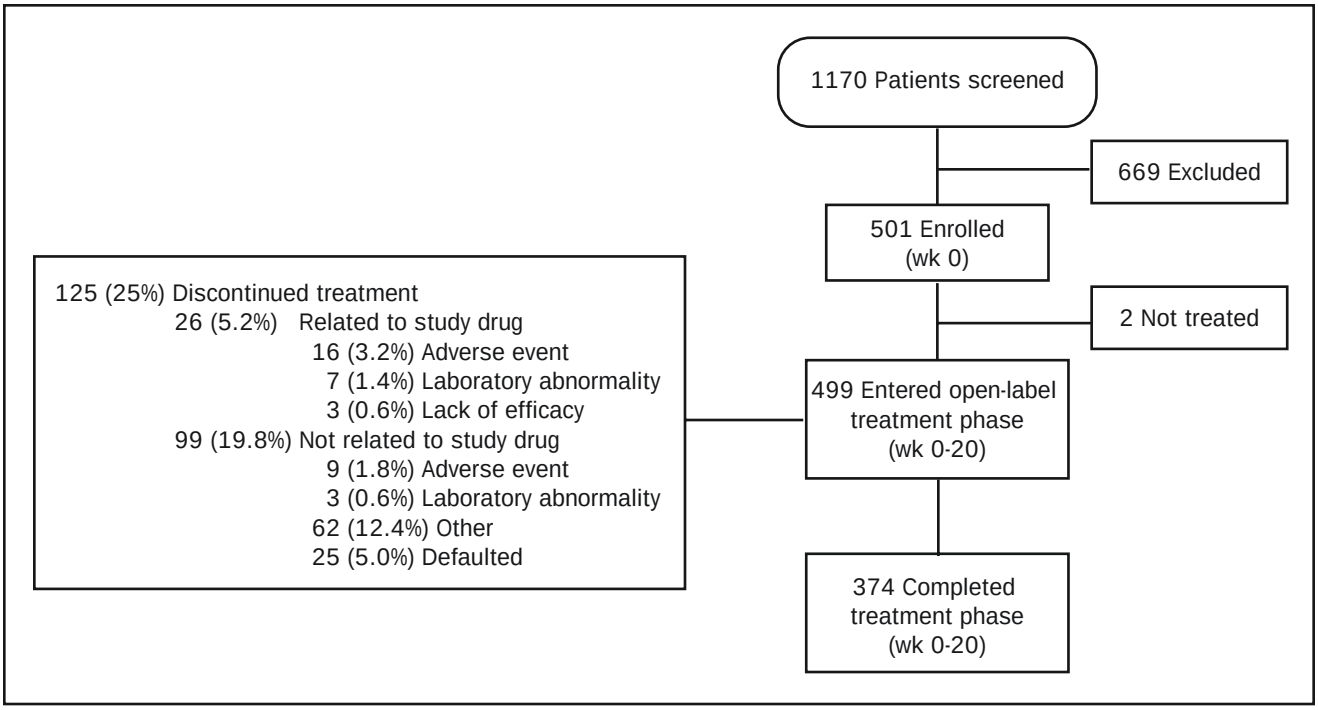

FIGURE 1. Flow of patients through the Clinical Utility of Caduet in Simultaneously Achieving Blood Pressure and Lipid End Points (CAPABLE) trial. "Other" included reasons such as protocol violation. "Patient defaulted" included reasons such as the patient being unwilling to continue in the study or being lost to follow-up.

continued for any reason (16 [3.2%] because of treatment-related AEs; Figure 1). Nine patients left the study within the first week of treatment and 28 by the end of the first month. Characteristics of the study participants are shown in Table 2.

Prior and Concomitant Medication

Of the 499 patients receiving study medication, 351 patients (70.3%) reported taking at least 1 antihypertensive drug and 227 (45.5%) a lipid-lowering agent (of these, 222 [97.8%] were receiving a statin) within the 6 weeks before study initiation. Within the 2 days before study initiation, the median number of antihypertensive drugs taken was 1, and 214 (42.9%) of 499 patients used a statin (Table 2). The antihypertensive drugs most commonly used during the treatment phase were angiotensin-converting enzyme inhibitors (170 [34.1%] of 499 patients), thiazides and related diuretics (101 [20.2%] of 499), β-blockers (98 [19.6%] of 499), angiotensin II receptor antagonists (70 [14.0%] of 499), and antihypertensive diuretic combinations (54 [10.8%] of 499).

Low-density lipoprotein cholesterol goals had been met at baseline in 19 (47.5%) of 40 patients previously treated with atorvastatin; in 84 (47.5%) of 177 patients previously treated with other statins; and in 35 (13.1%) of 267 patients previously treated with a lipid-lowering drug other than a statin. Blood pressure goals had been met at baseline in 0 patients previously treated with amlodipine, in 1 (1.3%) of 80 patients previously treated with other calcium channel blockers, and in 6 (1.5%) of 391 patients previously treated with an antihypertensive agent other than a calcium channel blocker. No more than 4 patients were at both goals at baseline in any category.

Mean Doses of Amlodipine/Atorvastatin

At study initiation, the mean dose of amlodipine/atorvastatin was 5.7/18.9 mg vs 8.2/26.4 mg at final visit. At end point, only 6.4% of patients received the highest dose of amlodipine/atorvastatin (10/80 mg), and 13% were still taking the lowest dose (5/10 mg).

BP and LDL-C Goal Attainment

Almost half of patients (236 [48.3%] of 489) attained both their BP and LDL-C goals (Figure 2, top). Dual goal attainment was higher in CV risk groups 1 and 2 than in group 3 (Figure 2, top) and was slightly lower (43.6%) in patients with uncontrolled LDL-C at baseline. The BP goal was achieved by 280 (56.8%) of 493 patients at end point (Figure 2, top). The trend across all CV risk groups was similar to that observed for joint goal attainment (Figure 2,

TABLE 2. **Patient Demographics and Baseline Values by Cardiovascular Risk Group and All Patients Combined**[a]

Characteristic	Group 1 (n=90)	Group 2 (n=164)	Group 3 (n=245)	Total (N=499)
Male, No. (%) of men	27 (30.0)	80 (48.8)	128 (52.2)	235 (47.1)
Age, y	50.3±11.2	53.8±9.90	58.3±10.5	55.4±10.8
Height, cm	166.8±10.7	170.6±11.2	169.7±9.9	169.5±10.6
Weight, kg	94.2±21.1	97.3±22.4	95.4±21.4	95.8±21.7
Diagnosed with diabetes mellitus, No. (%)	0 (0.0)	0 (0.0)	170 (69.4)	170 (34.1)
Receiving antihypertensive drugs at baseline, median No. of drugs (range)	1 (0-3)	1 (0-4)	2 (0-4)	1 (0-4)
Receiving statin therapy before trial, No. (%)	25 (27.8)	55 (33.5)	134 (54.7)	214 (42.9)
Baseline				
Blood pressure, mm Hg				
Systolic	147.9±12.5	149.1±11.3	146.0±11.5	147.4±11.7
Diastolic	93.7±7.7	93.7±7.2	88.6±7.7	91.2±7.9
Lipids, mg/dL[b]				
LDL-C	160.0±37.2	151.4±38.9	129.3±37.4	142.2±39.9
LDL-C uncontrolled at baseline	185.5±22.4	170.4±29.1	142.0±31.4	157.3±34.1
TC	240.0±39.7	226.0±43.0	204.5±42.9	218.1±44.6
HDL-C	59.8±12.2	50.0±11.0	51.4±13.5	52.5±13.0
Triglycerides	100.9±49.2	123.1±58.7	120.1±76.9	117.5±67.2
VLDL-C	20.1±9.8	24.6±11.8	23.0±12.4	23.0±11.8
ApoB	117.2±23.9	113.9±26.3	102.7±27.1	109.0±27.0

[a] Values are mean ± SD unless otherwise indicated. ApoB = lipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; VLDL-C = very low-density lipoprotein cholesterol.

[b] SI conversion factor: To convert cholesterol values to millimoles per liter, multiply by 0.0259; to convert triglyceride value to millimoles per liter, multiply by 0.0113; to convert ApoB value to grams per liter, multiply by 0.01.

top). The LDL-C goal was achieved by 361 (73.7%) of 490 patients in the ITT population (Figure 2, top) vs 235 (68.5%) of 343 with uncontrolled LDL-C at baseline.

Goal attainment was also assessed in the 374 patients (75.0%) who completed the study. In this population, joint BP and LDL-C goal attainment was higher than in the ITT group (54.5% vs 48.3%) (Figure 2, bottom). Similarly, higher goal attainment rates were also seen for BP alone (64.2% vs 56.8%) and LDL-C alone (78.6% vs 73.7%) in the group that completed the study (Figure 2, bottom).

Figure 3 shows the distribution of the SBP and LDL-C levels for all patients at baseline and end point, demonstrating the larger number of patients with joint goal attainment at end point vs baseline across all CV risk groups.

Blood pressure goal attainment was independent of prior therapy with amlodipine (52.2%), other calcium channel blockers (55.7%), or no calcium channel blockers (57.3%). Equivalent LDL-C goal attainment was observed in those who continued atorvastatin (60.0%), switched from another statin (72.9%), or received atorvastatin as initial therapy (76.2%), the 95% confidence intervals for the mean overlapping in each case.

Changes in BP and Lipids

Mean ± SD change from baseline in SBP and diastolic BP in the ITT study population was –17.5±14.8 mm Hg and –10.1±8.7 mm Hg, respectively; this trend was confirmed across all 3 CV risk groups with a slightly smaller change observed for CV risk group 3 (Table 3). Mean ± SD percentage change from baseline in LDL-C was –23.6±26.8% for ITT patients and –30.9±20.0% for patients with uncontrolled LDL-C at baseline; in both patient populations, the change in LDL-C was greatest in CV risk group 2 (Table 3). Mean percentage reductions from baseline in total cholesterol, triglycerides, very low-density lipoprotein cholesterol, and apolipoprotein B as well as increases in high-density lipoprotein cholesterol were observed (Table 3).

Titration Analysis of Patients Not at Goal for BP and LDL-C

To assess the titration patterns of amlodipine and atorvastatin, a post hoc analysis was conducted in patients who were not at goal for BP or LDL-C at each titration visit (weeks 4 [BP only], 6, 10, and 14; Figure 4). Of the 283 patients who were not at goal for BP, 109 (38.5%) received the maximal amlodipine dose (10 mg) at the first titration

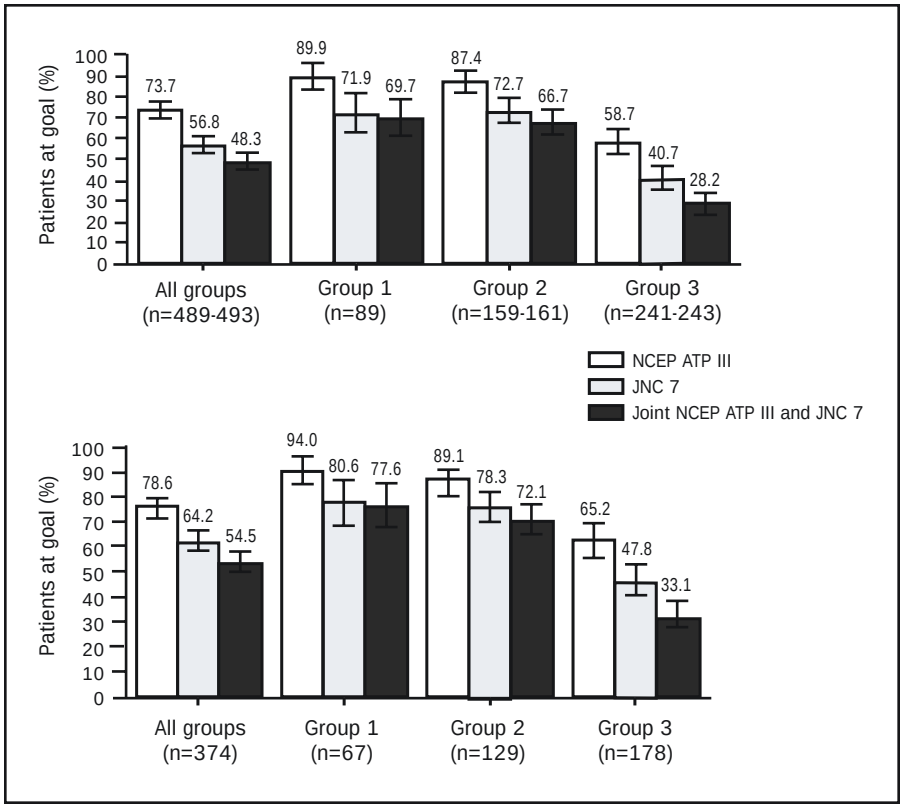

FIGURE 2. Of the intention-to-treat population (top) and of patients who completed the treatment phase of the trial (bottom), the percentage of patients who reached blood pressure and/or low-density lipoprotein cholesterol (LDL-C) goals at end point, analyzed by cardiovascular risk group. The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) blood pressure goals are as follows: group 1, <140/90 mm Hg; group 2, <140/90 mm Hg; and group 3, <130/80 mm Hg. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL-C goals for these risk groups are as follows: group 1, <160 mg/dL; group 2, <130 mg/dL; and group 3, <100 mg/dL. Last observations were carried forward for this analysis. Error bars represent 95% confidence intervals. There were multiple efficacy end points, and not all patients in the study population were evaluated for each therapeutic blood pressure and/or LDL-C goal; an n-value range is given, where applicable.

visit (week 4; Figure 4, top). Subsequently, the proportion of patients eligible for upward titration (ie, those not already taking the maximal dose) steadily decreased from 77 (36.0%) of 214 patients at week 6 to 25 (17.5%) of 143 patients at week 14. The dosage of amlodipine was increased in only 25 (32.5%) of the 77 patients taking a submaximal dose at week 6 and in only 9 (36.0%) of the 25 patients taking a submaximal dose at week 14.

Among patients who were not at goal for LDL-C (Figure 4, bottom), only a small proportion (3.6%-20.0%) received the highest dose of atorvastatin (80 mg). Throughout the study more than half of patients with uncontrolled LDL-C levels who were not already taking 80 mg of atorvastatin continued taking suboptimal doses of the atorvastatin component. This tendency was most evident in patients at highest risk for CV events (group 3); most patients (77%-81%) with uncontrolled LDL-C levels belonged to group 3. In group 3, no titration upward occurred in 48 (56.5%) of 85 patients, 49 (64.5%) of 76 patients, and 27 (47.4%) of 57 patients who were uncontrolled for LDL-C at weeks 6, 10 and 14, respectively.

Safety and Tolerability

Of the 499 patients included in the safety analysis, 35 patients (7.0%) were discontinued from the study because of AEs and laboratory test abnormalities, most of them mild or moderate in intensity. Only 16 patients (3.2%) were discontinued because of an AE that was considered by the investigator to be related to the study medication (Figure 1).

The most common (≥2% incidence) treatment-related AEs were peripheral edema (3.4%), headache (2.2%), myalgia (2.2%), and constipation (2.0%) (Table 4), none of which were considered severe.

Serious adverse events (SAEs) occurred in 19 patients (3.8%). Of these, 2 patients had SAEs that were considered to be related to the treatment (noncardiac chest pain and hepatic enzyme abnormalities). Four patients were discontinued from the study because of

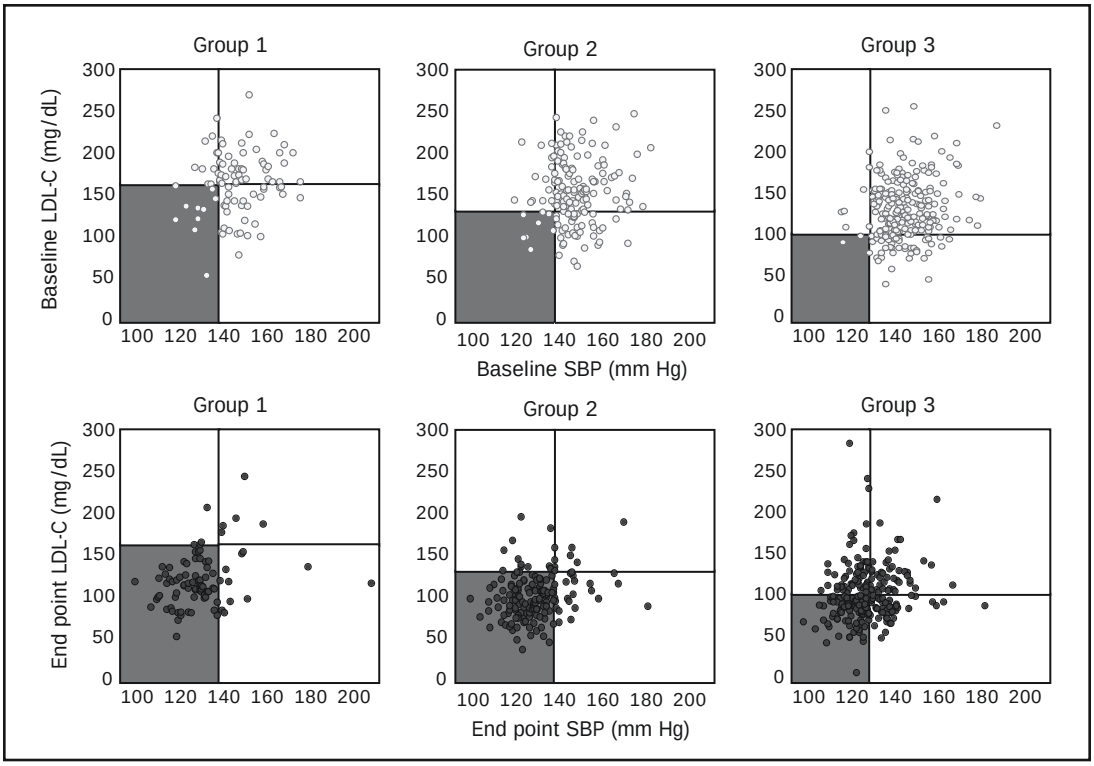

FIGURE 3. Distribution of systolic blood pressure (SBP) vs low-density lipoprotein cholesterol (LDL-C) values at baseline and at final visit for all intention-to-treat patients in the Clinical Utility of Caduet in Simultaneously Achieving Blood Pressure and Lipid End Points (CAPABLE) trial, analyzed by cardiovascular risk group. Vertical lines represent SBP goals and horizontal lines represent LDL-C goals for each of the 3 cardiovascular risk groups. The shaded quadrant represents attainment of joint SBP and LDL-C goals.

TABLE 3. **Change From Baseline in Blood Pressure and Various Lipid Parameters by Cardiovascular Risk Group and All Patients Combined**[a]

Changes from baseline	Group 1 (n=89)	Group 2 (n=161)	Group 3 (n=244)	Total (N=494)
Blood pressure, mm Hg				
Systolic	–17.9±16.6 (–21.4 to –14.4)	–18.2±13.8 (–20.3 to –16.0)	–17.0±14.9 (–18.9 to –15.1)	–17.5±14.8 (–18.8 to –16.2)
Diastolic	–10.1±9.1 (–12.0 to –8.2)	–10.8±8.7 (–12.1 to –9.4)	–9.7±8.6 (–10.8 to –8.7)	–10.1±8.7 (–10.9 to –9.4)
Lipids, %				
LDL-C	–22.5±31.6 (–29.2 to –15.8)	–29.5±20.9 (–32.8 to –26.1)	–20.1±27.7 (–23.6 to –16.5)	–23.6±26.8 (–26.0 to –21.2)
TC	–17.0±20.4 (–21.3 to –12.7)	–21.1±14.8 (–23.5 to –18.8)	–14.2±19.1 (–16.6 to –11.7)	–17.0±18.3 (–18.6 to –15.3)
HDL-C	+1.8±15.4 (–1.5 to 5.0)	+2.9±15.1 (0.5 to 5.3)	+2.0±18.4 (–0.4 to 4.3)	+2.2±16.8 (0.7 to 3.7)
Triglycerides	–8.7±39.3 (–17.0 to –0.4)	–8.8±39.1 (–15.0 to –2.6)	–4.9±54.1 (–11.9 to 2.0)	–6.9±47.0 (–11.1 to –2.6)
VLDL-C	–8.5±39.7 (–16.9 to –0.1)	–9.9±37.6 (–15.8 to –4.0)	–6.5±46.2 (–12.5 to –0.5)	–8.0±42.3 (–11.8 to –4.2)
ApoB	–20.1±23.0 (–24.9 to –15.2)	–24.0±17.1 (–26.7 to –21.2)	–16.0±23.1 (–19.0 to –13.0)	–19.3±21.6 (–21.3 to –17.4)
LDL-C[b]	–34.7±15.8 (–39.2 to –30.2)	–36.1±14.4 (–38.8 to –33.4)	–26.7±22.9 (–30.0 to –23.4)	–30.9±20.0 (–33.0 to –28.7)

[a] Values are shown as mean ± SD (95% confidence interval). ApoB = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; VLDL-C = very low-density lipoprotein cholesterol.

[b] Uncontrolled at baseline.

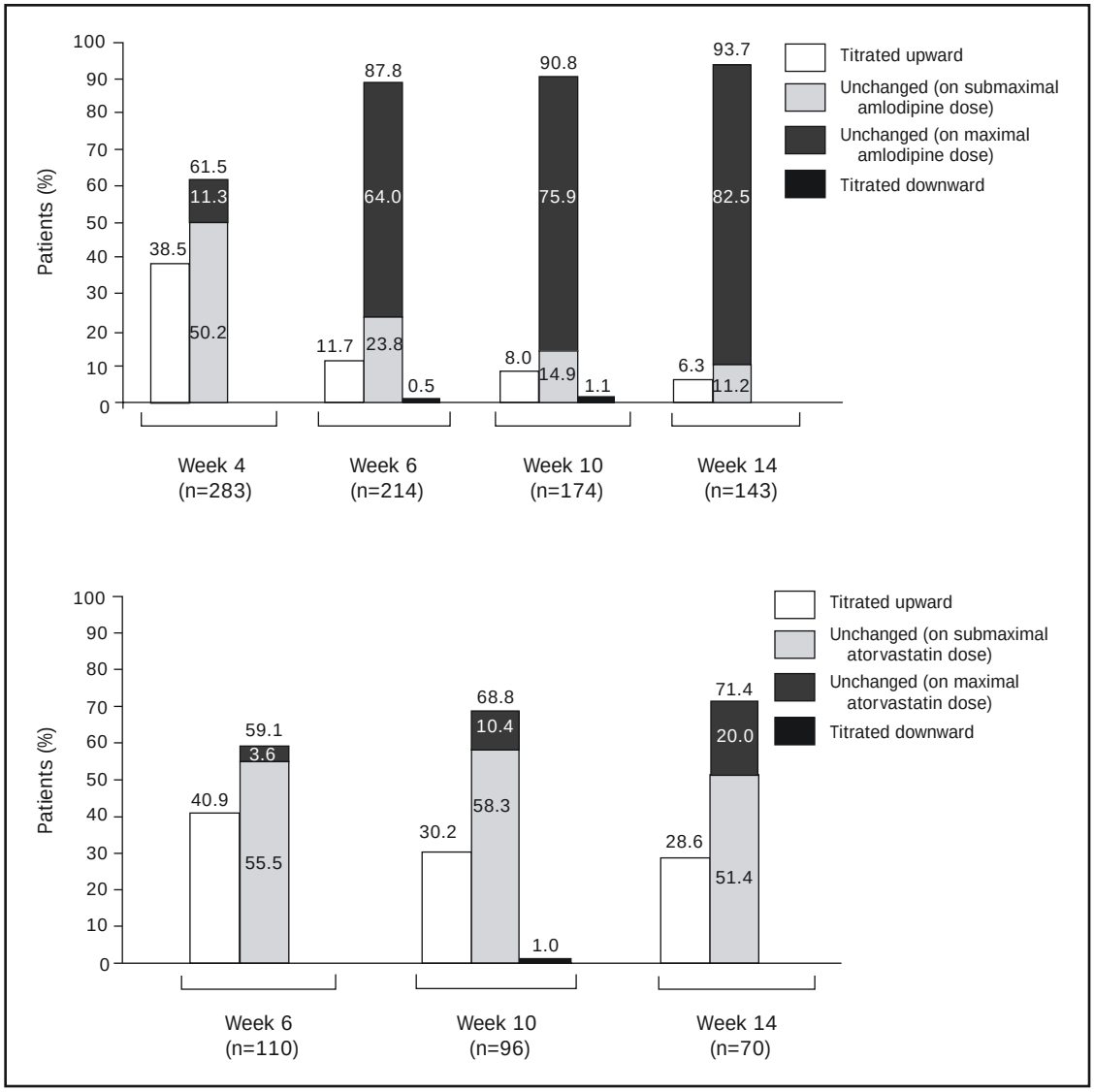

FIGURE 4. Titration patterns of patients who were not at goal for blood pressure (BP) (top) and not at goal for low-density lipoprotein cholesterol (LDL-C) (bottom) during the course of the trial. Top, Patients were included in this observational analysis if they were not at goal for BP as assessed by BP readings taken in the physician's office at the respective titration visit and if information on study drug dose and titration pattern were available at that visit. Titration patterns were determined at weeks 4, 6, 10, and 14. Week 20 is not shown because no upward or downward titration was permitted at that visit. Bottom, Patients were included in this observational analysis if they were not at goal for LDL-C based on the last available measurement of LDL-C (taken at weeks 4, 6, or 10) and if information on study drug dose and titration pattern was captured at the respective titration visit (weeks 6, 10, and 14). Weeks 4 and 20 are not shown because no upward or downward titration was permitted at these visits.

SAEs that were not thought to be related to amlodipine/atorvastatin. No patients died.

Clinical Laboratory Test Abnormalities

Of the 478 patients who had a baseline and at least 1 postbaseline CK measurement, 9 (1.9%) had CK levels on 1 occasion that were 5 to 10 times the ULN. No patient had CK levels that were persistently greater than 10 times the ULN; however, 2 patients (0.4%) had CK levels greater than 10 times the ULN on 1 occasion that decreased to less than 5 times the ULN on follow-up. Of these 2 patients, 1 had muscle cramps and myalgia that were considered unrelated to study treatment. Neither was discontinued from the study. An increase in CK was reported as a treatment-related AE in 22 (4.4%) of the 499 study patients.

TABLE 4. **Treatment-Related Adverse Events in 499 African American Patients**

Adverse event	No. (%) of patients
Peripheral edema	17 (3.4)
Headache	11 (2.2)
Myalgia	11 (2.2)
Constipation	10 (2.0)
Dizziness	9 (1.8)
Dyspepsia	7 (1.4)
Leg cramps	7 (1.4)
Back pain	5 (1.0)
Pain	4 (0.8)
Hypokalemia	4 (0.8)
Respiratory tract infection	3 (0.6)
Arthralgia	2 (0.4)
Cough increased	1 (0.2)
Any adverse event	282 (56.5)

Of the 479 treated patients with a baseline result and at least 1 postbaseline liver function test reading, 5 patients (1.0%) had ALT levels greater than 3 times the ULN; 4 (0.8%), AST levels greater than 3 times the ULN; 1 (0.2%), alkaline phosphatase levels greater than 3 times the ULN; 14 (2.9%), GGT levels greater than 3 times the ULN; and none, total bilirubin greater than 3 times the ULN. Persistent elevations in AST or ALT, defined as 2 consecutive measurements greater than 3 times the ULN within a 14-day period, were also analyzed to allow for comparison with other reports in the literature (these thresholds are in accordance with guidelines of the American College of Cardiology, the American Heart Association, and the National Heart, Lung, and Blood Institute[25]). Using these definitions, 4 patients (0.8%) were shown to have persistent ALT elevations greater than 3 times the ULN, 3 of whom also had persistent AST levels greater than 3 times the ULN. Of the 4 patients with persistent ALT or AST elevations, 3 patients withdrew from the study because of a laboratory test abnormality.

DISCUSSION

We have shown, in a study designed to approximate "real-world" practice in African Americans with poorly controlled HTN and dyslipidemia, that single-pill amlodipine/atorvastatin provides substantial improvement in both risk factors. Control of HTN and dyslipidemia had been achieved in fewer than 1% of patients at study entry but was attained by almost half by week 20. The single-pill combination was well tolerated.

Investigators had discretion to flexibly titrate the amlodipine and atorvastatin components of the single pill to prespecified BP and LDL-C goals based on accepted standards. However, even in the face of suboptimal goal attainment—most marked in those at highest risk—there was an apparent reluctance to titrate to higher doses, particularly for the statin component. More than half of patients who were not at goal for LDL-C remained on a submaximal dose of the atorvastatin component throughout. This was particularly evident in patients at the highest risk of CV events.

Of all treated patients, 48.3% reached both their BP and LDL-C therapeutic goals. Joint goal attainment was higher in CV risk groups 1 and 2 (69.7% and 66.7%, respectively) than in CV risk group 3 (28.2%), as might be expected given that target values were higher in groups 1 and 2 and more stringent in group 3. Group 3 patients were treated, as per protocol, to the lower JNC 7 BP values for patients with diabetes (<130/80 mm Hg), although 30.6% of patients in this group did not have diabetes. The difference between baseline and target values for SBP and LDL-C tended to be greater with increased risk.

The CAPABLE trial suggests, but does not confirm, that BP and LDL-C goals could be more difficult to attain in African Americans than in other ethnic/racial groups. Joint goal attainment in the CAPABLE trial (48.3%) was approximately 10% lower than in the Gemini trial (57.7%), a similar amlodipine/atorvastatin clinical utility study that focused on a predominantly non–African American population.[17] Joint goal attainment was lower in the CAPABLE trial even though it was longer than the Gemini trial (20 vs 14 weeks) and used higher mean doses of amlodipine/atorvastatin (8.2/26.4 mg vs 7.1/26.2 mg).[17] This lower goal attainment is not explained by differences between the studies in BP and LDL-C values at baseline. Although many of the study sites represent underserved urban African American communities, data on educational or socioeconomic status were not collected in either trial; thus, the relative contributions of these factors and ethnicity to the differences cannot be ascertained.

Single-pill amlodipine/atorvastatin therapy was well tolerated in this African American population. Although 25.1% of patients were discontinued from this trial, only 3.2% withdrew because of treatment-related AEs. Protocol violation accounted for 12.4% of discontinuations; another 5.0% of patients were unwilling to participate or were lost to follow-up. The overall discontinuation rate was higher than that of the Gemini trial (25.1% vs 10.2%).[17] This difference suggests, but again does not confirm, poorer adherence to antihypertensive and lipid-lowering therapy in the context of a clinical trial protocol in African Americans than in a predominantly white population.

The relatively high discontinuation rate observed in the CAPABLE trial likely influenced goal attainment in the ITT analysis. Nine patients discontinued study treatment in the first week. When only patients who completed the treat-

ment phase were examined, joint BP and LDL-C goal attainment rates increased to 54.5% (vs 57.7% in Gemini).

Individual goal attainment for BP was lower in this trial than that for LDL-C. This finding is understandable given the study design: eligible patients could not be at BP goal but could be at LDL-C goal. Although several antihypertensive agents are typically required to treat hypertensive patients to goal,[7,22] only the amlodipine component of the single pill could be titrated during the treatment phase. Most patients who were not at BP goal had received the highest dose of amlodipine (10 mg) (82.5% at week 14). Concomitant antihypertensive medications were permitted only at entry to the trial; thereafter, stable doses were maintained.

Upward titration of the atorvastatin component was less frequent than of the amlodipine component of the single-pill amlodipine/atorvastatin. Only a small percentage (≤20%) of patients in whom LDL-C levels were uncontrolled received the highest dose of atorvastatin (80 mg) in the CAPABLE trial; the remaining patients who were not at goal continued to receive submaximal doses of the lipid-lowering component. These figures suggest a greater comfort level with high-dose amlodipine vs atorvastatin and/or a relative degree of complacency regarding uncontrolled LDL-C vs BP. Because LDL-C goal attainment is related to atorvastatin dose,[26] intensification of therapy when clinically indicated could be reasonably assumed to result in greater goal attainment. Effective lipid management is critical to maximize the reduction of CV events in patients receiving antihypertensive therapy.[8,27] If CV events are to be effectively reduced, physicians must become aware that the need to treat to goal is as urgent for LDL-C as for BP.

The AE profile of single-pill amlodipine/atorvastatin therapy seen in the CAPABLE trial is comparable to that observed in the Gemini trial[17] and to the AE profile of coadministered amlodipine and atorvastatin in randomized, placebo-controlled trials.[15,16,28] The proportion of patients with CK abnormalities in the CAPABLE trial was generally higher than in the Gemini trial, as would be expected given reports that African Americans have higher CK levels than whites or Hispanics.[29]

African Americans are underrepresented in clinical trials of CV disease,[21] leading to uncertainties as to the benefit and safety of therapies that have been shown to be effective in other populations. Despite a particularly high risk of CV events in these patients, including stroke and end-stage renal disease,[30,31] modifiable risk factors remain underrecognized and undertreated.[3] Reduced access to medications and nonadherence to drug therapy are substantial barriers to goal attainment.[32] With the caveat that the adherence benefit from lower pill burden could be offset if the costs of single-pill combinations are higher, our study suggests that single-pill amlodipine/atorvastatin therapy could have considerable clinical utility and benefit in African American patients with concomitant HTN and dyslipidemia.

CONCLUSION

Blood pressure and LDL-C goals have been more difficult to attain in African Americans than in the overall US population. In our study, single-pill amlodipine/atorvastatin therapy was well tolerated and effectively targeted HTN and dyslipidemia in a population of African Americans who were at risk of cardiovascular disease. Our study suggests that there is reluctance among physicians to titrate to higher doses—particularly of statin.

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