

# Simultaneous treatment to attain blood pressure and lipid goals and reduced CV risk burden using amlodipine/atorvastatin single-pill therapy in treated hypertensive participants in a randomized controlled trial

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**Abstract:** TOGETHER investigated whether targeting multiple cardiovascular (CV) risk factors using single-pill amlodipine/atorvastatin (AML/ATO) and therapeutic lifestyle changes (TLC) results in greater blood pressure (BP)/lipid control and additional reduction in estimated cardiovascular disease (CVD) risk compared with blood pressure intervention only using amlodipine (AML) + TLC. TOGETHER was a 6-week, randomized, double-blind, double-dummy trial using hypertensive participants with additional CV risk factors without CVD/diabetes. Participants were randomized to either AML/ATO (5 to 10/20 mg) + TLC or AML (5 to 10 mg) + TLC. The primary end point was the difference in proportion of participants attaining both BP (<140/90 mm Hg) and low-density lipoprotein cholesterol (LDL-C) (<100 mg/dL) goals at week 6. At week 6, 67.8% of participants receiving AML/ATO + TLC attained the combined BP/LDL-C goal versus 9.6% with AML + TLC (RD [A–B]: 58.2; 95% CI [48.1 to 68.4]  $P < 0.001$ ; OR: 19.0; 95% CI 9.1 to 39.6;  $P < 0.001$ ). Significant reductions from baseline in LDL-C, total cholesterol and triglycerides and estimated 10-year Framingham risk were also observed. Treatment with AML/ATO was well tolerated. In conclusion, a multifactorial CV management approach is more effective in achieving combined BP/LDL-C targets as well as CV risk reduction compared with BP intervention only in this patient population.

**Keywords:** blood pressure, calcium channel blocker, low-density lipoprotein cholesterol, statin

## Introduction

Approximately one in three Americans are affected by cardiovascular disease (CVD).<sup>1</sup> Hypertension is an important modifiable cardiovascular (CV) risk factor that commonly clusters with other CV risk factors, such as dyslipidemia, smoking, and diabetes. These risk factors independently add to the overall risk of CV events.<sup>2</sup> Although patients with hypertension and additional CV risk factors could potentially benefit significantly from the treatment of their absolute CV risk,<sup>3</sup> the dominant paradigm in routine clinical practice is often focusing on each risk factor in isolation rather than simultaneously. There are many reasons for this isolated approach, both historical and practical, eg, current CV risk factor guidelines which traditionally have been focused on individual risk factors rather than taking an integrated approach addressing a patient's absolute CV risk; and concern about pill burden by physicians and patients.<sup>4,5</sup>

Concern about an increasing pill burden may also negatively affect adherence to co-administered antihypertensive and lipid-lowering medication;<sup>6</sup> in turn,

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improved adherence to co-administered antihypertensive and lipid-lowering therapy at levels seen in clinical trials may result in incremental cost savings compared with 'real-world' adherence levels.<sup>7</sup> By reducing pill burden, combination pills containing both an antihypertensive and a lipid-lowering agent may therefore improve the management of CV risk and improve the cost-effectiveness of the dual therapy.

Therapeutic lifestyle changes (TLC) are an integral part of current hypertension guidelines.<sup>4</sup> For patients at low to moderate CV risk, they recommend the use of pharmacotherapy if patients do not attain their blood pressure (BP) therapeutic goals through TLC alone.<sup>4</sup>

The aim of this randomized, double-blind, double-dummy, controlled trial was to investigate whether a multiple risk factor management strategy using AML/ATO single-pill therapy + TLC results in greater BP/lipid control than the traditional approach of BP intervention only using amlodipine + TLC, in patients at low-to-moderate CV risk who would not be identified as candidates for statin therapy by current guidelines.

## Methods

### Study participants

Participants who were enrolled in the trial were  $\geq 21$  years of age, had hypertension, but no history of CVD or diabetes, and had  $\geq 2$  of the following CV risk factors: age  $\geq 45$  years if male;  $\geq 55$  years if female; current smoker; a family history of premature coronary heart disease (CHD) in a first-degree relative; high-density lipoprotein cholesterol (HDL-C)  $< 40$  mg/dL ( $< 1.0$  mmol/L); or a waist circumference of 102 cm ( $\geq 40$  inches) if male or 88 cm ( $\geq 35$  inches) if female. All participants were previously treated with AML 5 mg, with BP either controlled or stage 1 hypertension (systolic BP [SBP]  $\leq 159$  mm Hg and diastolic BP [DBP]  $\leq 99$  mm Hg) or controlled BP at 10 mg of amlodipine, in addition to a fasting low-density lipoprotein cholesterol (LDL-C) level at screening of  $\geq 100$  mg/dL and  $\leq 170$  mg/dL. Participants were excluded if they had a history of CHD, stroke, pulmonary vascular disease, or any of the following medications  $< 14$  days prior to screening: lipid-lowering drugs; calcium channel blockers other than AML; or  $> 3$  antihypertensive agents (including AML).

### Trial design

TOGETHER was a 6-week, prospective, randomized, double-blind, double-dummy clinical trial conducted between January 15, 2007 and April 18, 2008 within 38 US clinical sites. Following screening, eligible participants were

randomized to either AML (5 to 10 mg) + TLC or AML/ATO single-pill therapy (5 to 10 mg/20 mg) + TLC (Figure 1). For operational reasons, participants in both treatment arms received a placebo: an amlodipine placebo in the amlodipine/atorvastatin single-pill therapy arm, and an amlodipine/atorvastatin single-pill placebo in the amlodipine arm.

Double-blinding occurred using a central web/telephone computer-based telorandomization system which dispensed two double-blind labeled bottles to participants at each dispensing visit (week 0 and week 4). Participants were instructed to take one tablet from each bottle per day at the same time daily. Randomized participants were stratified based on prior amlodipine dose and BP control, and those who were uncontrolled at 5 mg were uptitrated to 10 mg after randomization.

Blood pressure was measured using a digital blood pressure monitor at each visit. Following a seated resting period (10 to 30 min), three seated BP measurements were taken and the mean of these measurements was calculated.

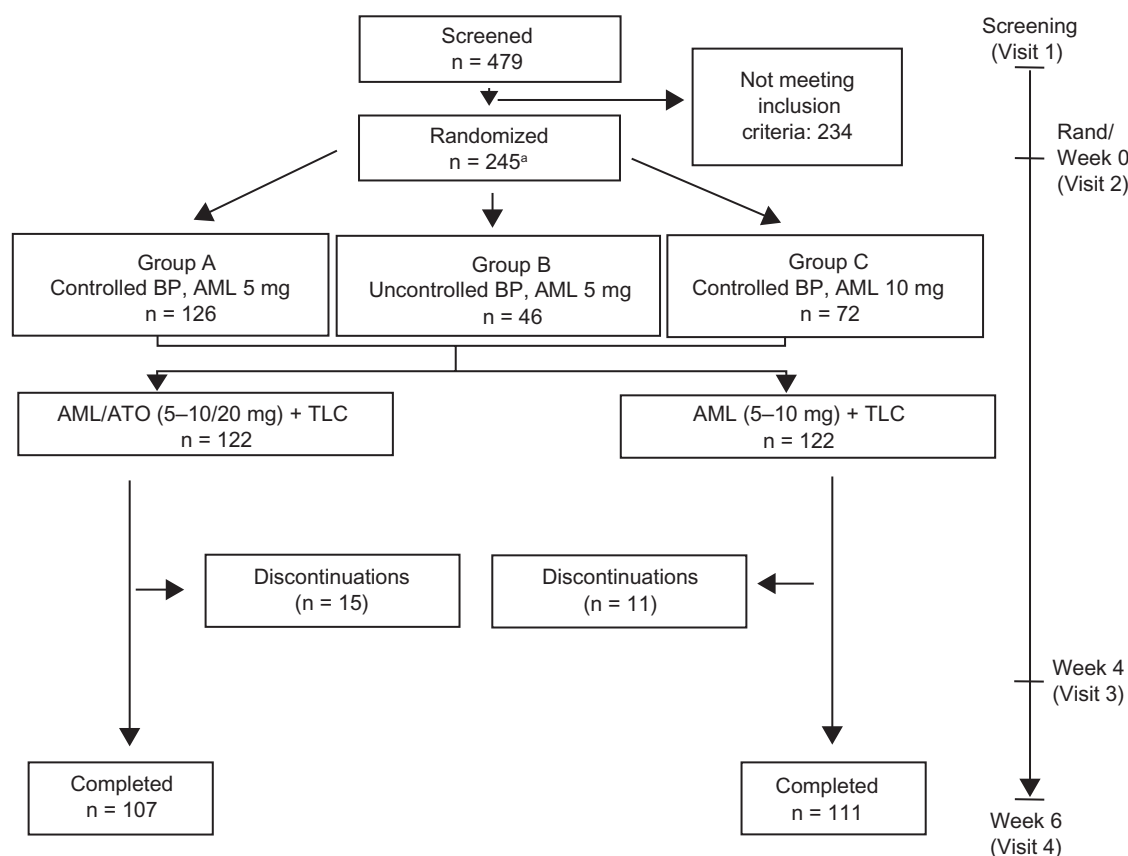
Serum lipid profiles (LDL-C, total cholesterol, triglycerides, and HDL-C) were determined at each visit. Participants were required to fast for 10 hours prior to the blood test, and were asked not to perform any vigorous exercise the day before the test.

Participants in each treatment arm were counseled on implementing TLC as outlined by the American Heart Association's Diet, Exercise and Smoking Cessation guidelines<sup>8</sup> at the start of the study for use throughout the entire duration of the trial.

### Efficacy measures

The primary end point in this study was the proportion of participants attaining a combined BP goal of  $< 140/90$  mm Hg as defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7)<sup>4</sup> and an optimal LDL-C level ( $< 100$  mg/dL) as defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III),<sup>9</sup> at week 6. The optimal LDL-C threshold of  $< 100$  mg/dL is a considerably more aggressive goal than the level recommended by NCEP ATP III for most patients in this study population.

Secondary end points in this study included the proportion of participants attaining a combined BP goal of  $< 140/90$  mm Hg and an LDL-C goal of  $< 100$  mg/dL at week 4; the proportion of participants attaining the LDL-C goal of  $< 100$  mg/dL at weeks 4 and 6; the proportion of participants attaining the BP goal of  $< 140/90$  mm Hg at weeks 4 and 6; change



**Figure 1** Trial design and flow of participants through the trial.

**Notes:** <sup>a</sup>One participant was randomized, but did not receive any study medication, and was excluded from all analyses. Group A, prior amlodipine 5 mg + controlled BP; Group B, prior amlodipine 5 mg + uncontrolled BP; Group C, prior amlodipine 10 mg + controlled BP.

**Abbreviations:** AML, amlodipine; ATO, atorvastatin; TLC, therapeutic lifestyle changes.

from baseline in SBP, DBP, LDL-C, total cholesterol (TC), triglycerides, and HDL-C at weeks 4 and 6; the predicted 10-year Framingham risk of CHD outcomes<sup>10</sup> at weeks 4 and 6; and the safety profile of the AML/ATO single-pill regimen + TLC compared with the AML + TLC regimen. The efficacy population was defined as all randomized participants who took at least one dose of study drug and for whom at least one post-baseline efficacy measurement was available. The safety population was defined as all randomized participants who took at least one dose of study drug.

## Adverse events

Adverse events (AEs) were monitored and recorded by the investigator from the time participants took at least one dose of study medication until the end of the treatment period. AEs were summarized by treatment group and severity, and encoded to a system organ class according to the Medical Dictionary for Regulatory Affairs (MedDRA), version 11.0. The investigator also assessed the causal relationship of the AE to the study medication. For any AE considered related

to the study medication, follow-up by the investigator was required until the AE ceased or stabilized to levels deemed acceptable by the investigator.

## Statistical analysis

Originally, 260 participants were estimated to be required for randomization, assuming a response rate of 35% for the primary efficacy measure in the AML/ATO + TLC arm, 15% in the AML + TLC arm, and a discontinuation rate of no more than 5%, at a significance level of 5% to provide 90% power. The number of randomized participants (n = 245) was considered sufficient, based on the actual treatment effect from a trial with a similar population and design.<sup>11</sup>

An intent-to-treat (ITT) analysis was conducted including participants who discontinued from the trial during the treatment period. Last observations from the non-completers were carried forward for final analysis. One participant randomized to AML + TLC did not take any study drug and no data were available for this individual beyond the baseline visit. This patient was excluded from any analyses.

For the primary end point analysis, odds ratios (OR), 95% confidence intervals (CI), and the corresponding *P*-values were calculated based on a Cochran-Mantel-Haenszel (CMH) test stratified by baseline amlodipine dose and BP control. For the mean change from baseline data, difference in least-square (LS) means, its 95% CI, and the corresponding *P*-values were based on an analysis of covariance (ANCOVA) model with terms for treatment group, randomization stratum, and baseline values as explanatory variables in the model.

## Results

### Baseline demographics

In total, 245 participants were randomized to the two treatment arms (Figure 1). However, one randomized participant in the AML + TLC arm did not take any study medication and was excluded from all analyses. Of the 244 participants who took study medication, *n* = 111 and *n* = 107 completed the trial in

the AML + TLC and AML/ATO + TLC arms, respectively (Figure 1). The mean age of participants was 56 years (ranging from 24 to 84 years), with more than half of them being white (Table 1). There were no significant differences in BP, lipid, and 10-year Framingham CHD risk at baseline between participants in the two treatment arms (Table 1).

### BP and LDL-C goal attainment

The proportion of participants attaining combined SBP/ LDL-C goal at week 6 (ie, the primary end point) was 9.6% in the AML + TLC arm, and 67.8% in the AML/ATO + TLC arm (RD [A–B]: 58.2; 95% CI [48.1 to 68.4]; *P* < 0.001; OR, 19.0; 95% CI [9.1 to 39.6]; *P* < 0.001; Figure 2). This difference was already apparent at week 4, when 5.2% participants on the AML + TLC-based regimen attained the combined goal compared with 62.9% participants receiving AML/ATO single-pill therapy, along with TLC

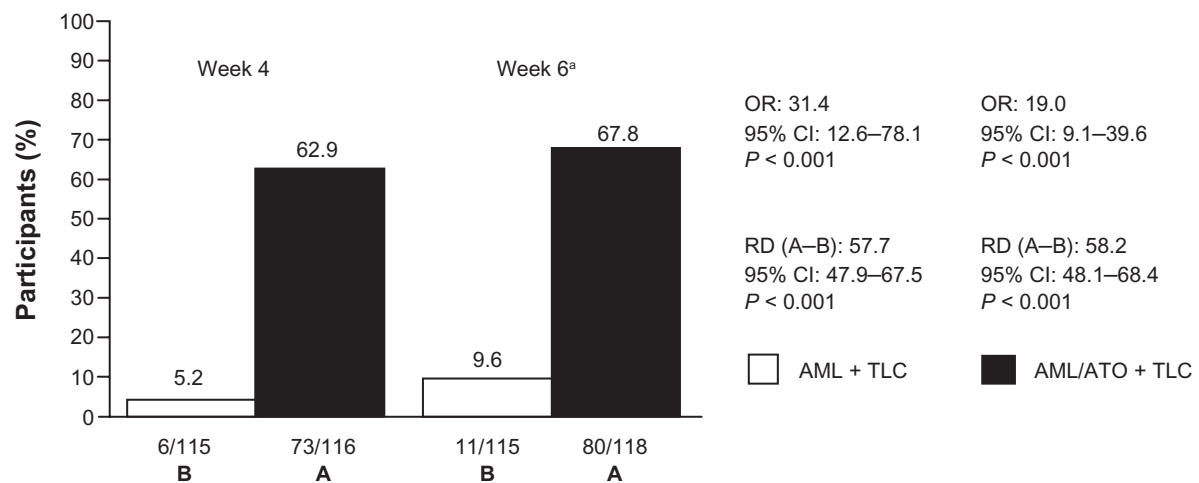
**Table 1** Baseline demographic characteristics<sup>a</sup>

|   | AML + TLC (n = 122) | AML/ATO + TLC (n = 122) | <i>P</i> -values <sup>b</sup> |
|---|---------------------|-------------------------|-------------------------------|
| Age, years, mean (range)                                | 55.5 (33–80)        | 56.5 (24–84)            | 0.43                          |
| Race, n (%)   |                     |                         | 0.92                          |
| White   | 62 (50.8)           | 63 (51.6)               | –                             |
| Black   | 38 (31.1)           | 39 (32.0)               | –                             |
| Asian   | 10 (8.2)            | 11 (9.0)                | –                             |
| Other   | 12 (9.8)            | 9 (7.4)                 | –                             |
| Gender, n (%)   |                     |                         | 0.25                          |
| Male  | 66 (54.1)           | 57 (46.7)               | –                             |
| Female  | 56 (45.9)           | 65 (53.3)               | –                             |
| Smoking status, n (%)                                   |                     |                         | 0.44                          |
| Never smoked  | 55 (45.1)           | 65 (53.3)               | –                             |
| Ex-smoker   | 27 (22.1)           | 23 (18.9)               | –                             |
| Current smoker  | 40 (32.8)           | 34 (27.9)               | –                             |
| SBP, mm Hg, mean (SD)                                   | 132.9 (12.3)        | 132.3 (11.3)            | 0.71                          |
| DBP, mm Hg, mean (SD)                                   | 81.9 (8.2)          | 81.0 (9.5)              | 0.42                          |
| LDL-C, mg/dL, mean (SD)                                 | 131.5 (24.7)        | 127.4 (21.7)            | 0.17                          |
| TC, mg/dL, mean (SD)                                    | 214.0 (30.7)        | 209.5 (29.7)            | 0.24                          |
| Triglycerides, mg/dL, mean (SD)                         | 137.6 (80.9)        | 140.4 (99.5)            | 0.81                          |
| HDL-C, mg/dL, mean (SD)                                 | 55.5 (16.1)         | 54.7 (17.5)             | 0.74                          |
| 10-year Framingham risk for CHD, <sup>10</sup> mean (%) | 8.5 (6.8)           | 8.3 (7.6)               | 0.77                          |
| Stratum, n (%)  |                     |                         |                               |
| Group A   | 63 (51.6)           | 63 (51.6)               | >0.99                         |
| Group B   | 23 (18.9)           | 23 (18.9)               |                               |
| Group C   | 36 (29.5)           | 36 (29.5)               |                               |

**Notes:** <sup>a</sup>For the safety population; <sup>b</sup>For categorical variables calculated based on approximate chi-square test; for continuous variables based on a *t*-test.

Group A, prior amlodipine 5 mg + controlled BP; Group B, prior amlodipine 5 mg + uncontrolled BP; Group C, prior amlodipine 10 mg + controlled BP.

**Abbreviations:** AML, amlodipine; ATO, atorvastatin; TLC, therapeutic lifestyle changes; SD, standard deviation; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol.



**Figure 2** Attainment of combined BP/LDL-C goal.

**Notes:** <sup>a</sup>Primary efficacy measure. The BP goal used in this analysis was  $<140/90$  mm Hg described by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.<sup>4</sup> The LDL-C goal used was 100 mg/dL, an optimal threshold defined by the National Cholesterol Education Program Adult Treatment Panel III.<sup>9</sup>

**Abbreviations:** AML, amlodipine; ATO, atorvastatin; OR, odds ratio; RD, risk difference; TLC, therapeutic lifestyle changes.

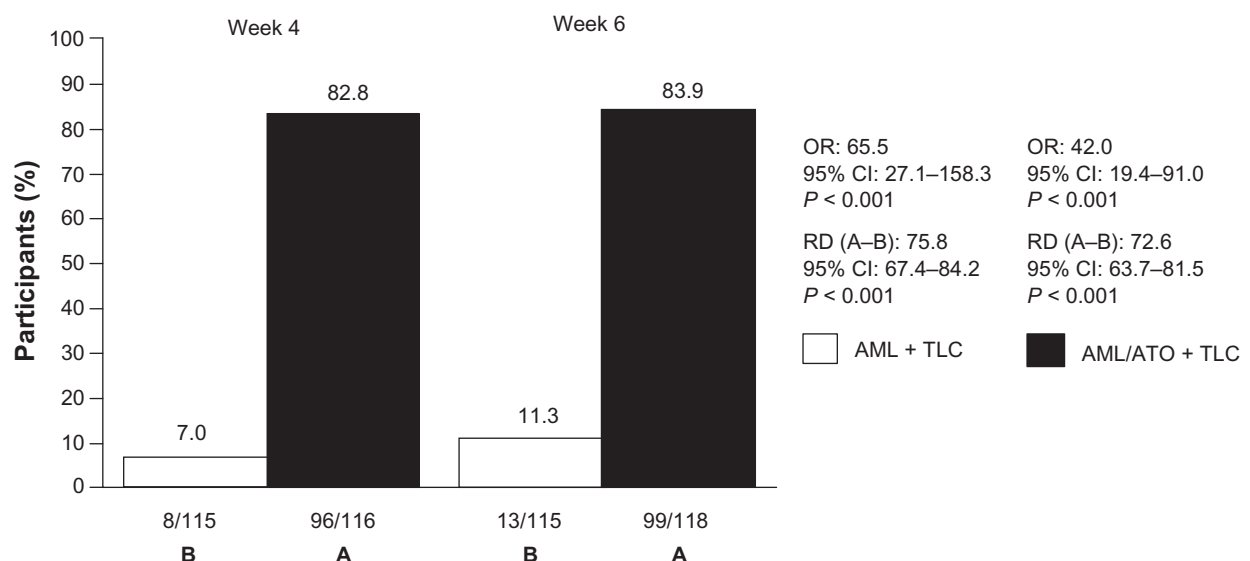
(RD [A–B]: 57.7; 95% CI [47.9 to 67.5];  $P < 0.001$ ; OR, 31.4; 95% CI [12.6 to 78.1];  $P < 0.001$ ; Figure 2).

LDL-C goal was achieved by 7.0% in the AML + TLC arm at week 4 compared with 82.8% participants in the AML/ATO + TLC arm (RD [A–B]: 75.8; 95% CI [67.4 to 84.2];  $P < 0.001$ ; OR 65.5; 95% CI [27.1 to 158.3];  $P < 0.001$ ; Figure 3); at week 6, 11.3% in the AML + TLC arm were at LDL-C goal versus 83.9% participants on the single-pill combination along with TLC (RD [A–B]: 72.6; 95% CI [63.7 to 81.5];  $P < 0.001$ ; OR, 42.0; 95% CI [19.4

to 91.0];  $P < 0.001$ ; Figure 3). The difference in combined SBP/DBP goal attainment between the two treatment arms was not significant (Figure 4); however, a 3.3 mm Hg difference in LS means in SBP at week 6 between the two groups was observed (Table 2).

### Mean changes from baseline in lipids, SBP/DBP, and 10-year Framingham risk

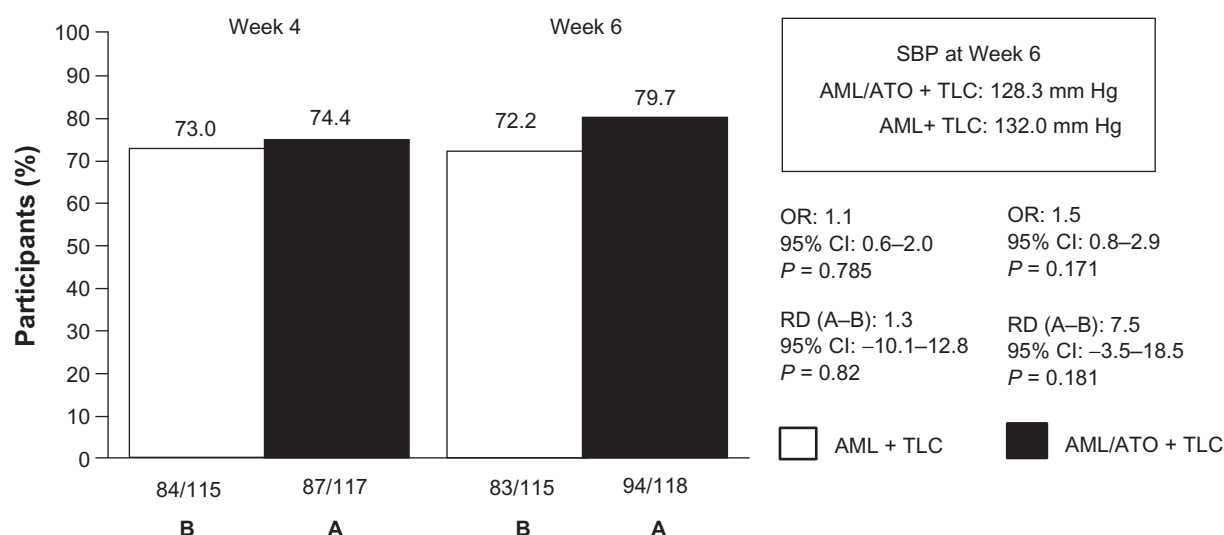
There were significant mean percentage reductions from baseline in LDL-C, TC, and triglycerides in the AML/ATO + TLC



**Figure 3** Attainment of LDL-C goal.

**Notes:** The LDL-C goal used for this analysis was  $<100$  mg/dL, an optimal threshold defined by the National Cholesterol Education Program Adult Treatment Panel III.<sup>9</sup>

**Abbreviations:** AML, amlodipine; ATO, atorvastatin; OR, odds ratio; RD, risk difference; TLC, therapeutic lifestyle changes.



**Figure 4** Attainment of SBP/DBP goal.

**Notes:** The SBP/DBP goal used in this analysis was <140/90 mm Hg described by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.<sup>4</sup>

**Abbreviations:** AML, amlodipine; ATO, atorvastatin; OR, odds ratio; RD, risk difference; TLC, therapeutic lifestyle changes; SBP, systolic blood pressure; DBP, diastolic blood pressure.

arm compared with the AML + TLC arm at weeks 4 and 6 (Table 2). There was no difference in DBP between the two treatment groups and no difference in SBP at week 4. However, at week 6 the difference in LS means in SBP was 3.3 mm Hg lower in the AML/ATO arm compared with the AML arm ( $P = 0.02$ ; Table 2).

In the AML/ATO + TLC arm, the 10-year Framingham risk for CHD at baseline was 8.2% and was reduced to 5.5% and 5.4% at week 4 and week 6, respectively, compared with the AML + TLC arm in which the 10-year Framingham risk was 8.1% at baseline and remained unchanged at week 6. At week 4, the percentage relative reduction from baseline in 10-year Framingham risk for CHD in participants on AML/ATO + TLC was 39.6%, compared with a percentage relative increase of 0.6% in participants on AML + TLC. At week 6, the corresponding percentage relative reduction from baseline was 42.0% in the AML/ATO + TLC arm compared with a percentage relative increase of 4.5% in the AML + TLC arm (Table 2).

## Safety and tolerability

Of the 244 participants who were included in the safety analysis, 4 discontinued from the trial due to an adverse event or laboratory abnormality, all of which in the AML/ATO + TLC arm (Table 3). Of these, 3 participants had AEs which were considered related to study medication: one discontinued due to mild abdominal pain, one due to severe tinnitus, and a third due to moderate abdominal pain and joint sprain.

There were no deaths or serious AEs reported during the conduct of the trial. Overall, treatment-related AEs occurred in 18 (14.8%) and 11 (9.0%) of participants in the AML + TLC and AML/ATO + TLC treatment arms, respectively. The majority of events in both arms were mild. Changes in liver function test and creatine phosphokinase were mild to moderate and similar in incidence and severity with previous reports and known profile of the study medication.

## Discussion

In clinical practice, patients with hypertension and additional CV risk factors are usually treated in isolation, ie, by initially focusing on treating their BP, and treating another CV risk factor only after the patient's BP has been controlled, thereby leaving the patient exposed to considerable residual CV risk in the interim. These results show that simultaneous treatment of BP and lipids using AML/ATO single-pill therapy, along with TLC, provides significant and rapid benefits for helping patients attain their combined BP and lipid goals, with a greater reduction in absolute 10-year Framingham risk for CHD outcomes, compared with an approach based on current guideline recommendations<sup>4</sup> using AML + TLC only.

As expected, significant improvements were observed in attaining LDL-C goals (<100 mg/dL). In fact, in this population LDL-C, not BP, was the driving factor behind the significant benefits that were observed for combined BP/LDL-C goal attainment, presumably as participants



**Table 2** Mean (95% CI) changes from baseline in SBP/DBP, various lipid parameters and 10-year Framingham risk for CHD outcomes

|                          | Week 4               |                         |          |                                 | Week 6               |                         |                                 |          |
|--------------------------|----------------------|-------------------------|----------|---------------------------------|----------------------|-------------------------|---------------------------------|----------|
|                          | Observed mean        |                         | P-values | Difference in LS means (95% CI) | Observed mean        |                         | Difference in LS means (95% CI) | P-values |
|                          | AML + TLC (n = 115)  | AML/ATO + TLC (n = 117) |          |                                 | AML + TLC (n = 115)  | AML/ATO + TLC (n = 118) |                                 |          |
| <b>SBP</b>               |                      |                         |          |                                 |                      |                         |                                 |          |
| Baseline (mm Hg)         | 133.0 (130.7, 135.2) | 132.4 (130.2, 134.4)    | –        | –                               | 133.0 (130.7, 135.2) | 132.3 (130.2, 134.4)    | –                               | –        |
| Mean changes (mm Hg)     | –2.6 (–4.8, –0.4)    | –1.5 (–3.7, 0.6)        | 0.585    | 0.8 (–2.0, 3.5)                 | –1.0 (–3.3, 1.3)     | –4.0 (–6.0, –2.0)       | –3.3 (–6.0, –0.5)               | 0.02     |
| <b>DBP</b>               |                      |                         |          |                                 |                      |                         |                                 |          |
| Baseline (mm Hg)         | 81.8 (80.3, 83.3)    | 81.0 (79.2, 82.7)       | –        | –                               | 81.8 (80.3, 83.3)    | 80.9 (79.2, 82.7)       | –                               | –        |
| Mean changes (mm Hg)     | –1.5 (–2.9, –0.1)    | –1.2 (–2.8, 0.4)        | >0.999   | –0.0 (–2.0, 2.0)                | –1.1 (–2.4, 0.3)     | –1.7 (–3.2, 0.2)        | –0.9 (–2.7, 1.0)                | 0.35     |
| <b>LDL-C</b>             |                      |                         |          |                                 |                      |                         |                                 |          |
| Baseline (mg/dL)         | 131.1 (126.5, 135.7) | 127.2 (123.3, 131.2)    | –        | –                               | 131.1 (126.5, 135.7) | 127.2 (123.3, 131.2)    | –                               | –        |
| Mean changes (mg/dL)     | –0.5 (–4.7, 3.8)     | –47.8 (–52.3, –43.3)    | <0.001   | –49.3 (–54.7, –43.9)            | 0.3 (–4.3, 4.9)      | –49.2 (–53.5, –44.8)    | –51.2 (–56.9, –45.6)            | <0.001   |
| Percentage change (%)    | 1.6 (–2.0, 5.2)      | –37.1 (–40.3, –33.8)    | <0.001   | –39.8 (–44.3, –35.2)            | 2.0 (–1.8, 5.7)      | –38.1 (–41.4, –34.8)    | –41.1 (–45.8, –36.3)            | <0.001   |
| <b>Total cholesterol</b> |                      |                         |          |                                 |                      |                         |                                 |          |
| Baseline (mg/dL)         | 213.6 (207.9, 219.4) | 208.8 (203.4, 213.9)    | –        | –                               | 213.6 (207.9, 219.4) | 208.7 (203.4, 213.9)    | –                               | –        |
| Mean changes (mg/dL)     | 0.5 (–3.8, 4.8)      | –55.9 (–60.8, –51.0)    | <0.001   | –57.9 (–64.0, –51.8)            | 3.7 (–0.6, 8.1)      | –56.8 (–62.0, –51.7)    | –62.1 (–68.5, –55.7)            | <0.001   |
| Percentage change (%)    | 0.9 (–1.3, 3.0)      | –26.6 (–28.8, –24.4)    | <0.001   | –28.0 (–31.0, –25.0)            | 2.2 (0.1, 4.3)       | –26.9 (–29.3, –24.5)    | –29.5 (–32.7, –26.4)            | <0.001   |
| <b>Triglycerides</b>     |                      |                         |          |                                 |                      |                         |                                 |          |
| Baseline (mg/dL)         | 135.7 (120.9, 150.6) | 138.8 (121.3, 154.5)    | –        | –                               | 135.7 (120.9, 150.6) | 137.9 (121.3, 154.5)    | –                               | –        |
| Mean changes (mg/dL)     | 2.4 (–11.1, 16.0)    | –45.7 (–57.2, –34.1)    | <0.001   | –47.3 (–63.4, –31.2)            | 11.6 (–9.7, 32.9)    | –42.6 (–54.9, –30.3)    | –54.0 (–77.6, –30.3)            | <0.001   |
| Percentage change (%)    | 4.3 (–3.5, 12.0)     | –24.6 (–30.1, –19.2)    | <0.001   | –28.6 (–37.8, –19.4)            | 10.1 (0.8, 19.5)     | –20.8 (–26.9, –14.7)    | –30.7 (–41.5, –19.9)            | <0.001   |

(Continued)

Table 2 (Continued)

|                                       | Week 4                 |                            |                                    |          | Week 6                 |                            |                                    |          |
|---------------------------------------|------------------------|----------------------------|------------------------------------|----------|------------------------|----------------------------|------------------------------------|----------|
|                                       | Observed mean          |                            |                                    | P-values | Observed mean          |                            |                                    | P-values |
|                                       | AML + TLC<br>(n = 115) | AML/ATO + TLC<br>(n = 117) | Difference in LS<br>means (95% CI) |          | AML + TLC<br>(n = 115) | AML/ATO + TLC<br>(n = 118) | Difference in LS<br>means (95% CI) |          |
| HDL-C                                 |                        |                            |                                    |          |                        |                            |                                    |          |
| Baseline<br>(mg/dL)                   | 55.8 (52.8, 58.8)      | 54.3 (51.3, 57.4)          | –                                  | –        | 55.8 (52.8, 58.8)      | 54.3 (51.3, 57.4)          | –                                  | –        |
| Mean changes<br>(mg/dL)               | 0.6 (–0.5, 1.7)        | 0.6 (–1.0, 2.1)            | –0.3 (–2.1, 1.5)                   | 0.739    | 1.2 (–0.5, 1.7)        | 0.4 (–1.0, 2.1)            | –1.0 (–3.1, 1.0)                   | 0.329    |
| Percentage<br>change (%)              | 2.0 (0.0, 4.0)         | 2.8 (0.0, 5.6)             | 0.5 (–2.8, 3.7)                    | 0.781    | 3.1 (0.7, 5.5)         | 1.6 (–0.9, 4.1)            | –1.8 (–5.1, 1.5)                   | 0.289    |
| 10-year Framingham risk <sup>10</sup> |                        |                            |                                    |          |                        |                            |                                    |          |
| Baseline<br>(mg/dL)                   | 8.1 (6.9, 9.3)         | 8.2 (6.9, 9.5)             | –                                  | –        | 8.1 (6.9, 9.3)         | 8.2 (6.9, 9.5)             | –                                  | –        |
| Mean changes<br>(mg/dL)               | –0.3 (–0.8, 0.1)       | –2.8 (–3.4, –2.2)          | –2.4 (–3.1, –1.7)                  | <0.001   | –0.1 (–0.6, 0.5)       | –2.9 (–3.4, –2.3)          | –2.8 (–3.5, –2.1)                  | <0.001   |
| Percentage<br>change (%)              | 0.6 (–6.7, 7.9)        | –39.6 (–44.4, –34.7)       | –40.1 (–48.9, –31.4)               |          | 4.5 (–3.2, 12.1)       | –42.0 (–46.9, –37.1)       | –46.5 (–55.6, –37.5)               | <0.001   |

**Notes:** Values are shown as mean  $\pm$  SD (95% confidence intervals). Full Analysis Set population used. Calculated based on an analysis of covariance (ANCOVA) model that includes value at a given time point as the response variable and treatment group, randomization strata, baseline value as explanatory variable.

'Baseline' row denotes the mean of individual measurements at baseline for each treatment group; 'mean changes' at week 4 are calculated as the average of (week 4 value – baseline value) for each treatment group. Similarly, 'mean changes' at week 6 are calculated.

**Abbreviations:** AML, amlodipine; ATO, atorvastatin; TLC, therapeutic lifestyle changes; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation.



**Table 3** Treatment-emergent all-causality adverse events by system organ class

|   | <b>All-causality</b>                      |   |
|---|---|---|
|   | <b>AML + TLC</b><br><b>n = 122, n (%)</b> | <b>AML/ATO + TLC</b><br><b>n = 122, n (%)</b> |
| With adverse events   | 37 (30.3)                                 | 34 (27.9)                                     |
| Discontinued due to adverse events/laboratory abnormalities | 0 (0.0)                                   | 4 (3.3)                                       |
| <b>System organ class</b>                                   |   |   |
| Blood and lymphatic system disorders                        | 0 (0.0)                                   | 1 (0.8)                                       |
| Cardiac disorders   | 0 (0.0)                                   | 1 (0.8)                                       |
| Ear and labyrinth disorders                                 | 2 (1.6)                                   | 1 (0.8)                                       |
| Eye disorders   | 2 (1.6)                                   | 0 (0.0)                                       |
| Gastrointestinal disorders                                  | 1 (0.8)                                   | 6 (4.9)                                       |
| General disorders and administration site conditions        | 9 (7.4)                                   | 5 (4.1)                                       |
| Hepatobiliary disorders                                     | 0 (0.0)                                   | 1 (0.8)                                       |
| Immune system disorders                                     | 0 (0.0)                                   | 1 (0.8)                                       |
| Infections and infestations                                 | 9 (7.4)                                   | 7 (5.7)                                       |
| Injury, poisoning, and procedural complications             | 0 (0.0)                                   | 1 (0.8)                                       |
| Investigations  | 6 (4.9)                                   | 3 (2.5)                                       |
| Metabolism and nutritional disorders                        | 1 (0.8)                                   | 0 (0.0)                                       |
| Musculoskeletal and connective tissue disorders             | 6 (4.9)                                   | 7 (5.7)                                       |
| Nervous system disorders                                    | 1 (0.8)                                   | 5 (4.1)                                       |
| Psychiatric disorders                                       | 1 (0.8)                                   | 2 (1.6)                                       |
| Renal and urinary disorders                                 | 2 (1.6)                                   | 0 (0.0)                                       |
| Respiratory, thoracic and mediastinal disorders             | 1 (0.8)                                   | 1 (0.8)                                       |
| Skin and subcutaneous disorders                             | 2 (1.6)                                   | 2 (1.6)                                       |
| Vascular disorders  | 7 (5.7)                                   | 3 (2.5)                                       |

**Abbreviations:** AML, amlodipine; ATO, atorvastatin; TLC, therapeutic lifestyle changes; BP, blood pressure.

were already receiving amlodipine prior to the trial, and consequently any additional improvements in BP goal attainment by the single-pill combination were minor, since BP treatment was equally optimized between the two arms (data not shown). The LDL-C threshold of <100 mg/dL is a considerably more aggressive goal than the one recommended by NCEP ATP III for most patients in this population. The decision to implement the LDL-C goal of <100 mg/dL for every patient in this population was made for operational reasons, as it is not possible to preserve the blind with individually determined therapeutic goals.

The effect of the atorvastatin component of the single-pill combination on LDL-C is also most likely the driving force behind the 2.8% percentage point drop in LS means in the 10-year Framingham risk for CHD events within 6 weeks seen in this trial. There was no percentage reduction in LS means in the 10-year Framingham risk in the AML + TLC arm, presumably because patients had been previously treated

with amlodipine, as stated above. This demonstrates that a simultaneous treatment approach using single-pill AML/ATO reduces CV risk burden in this population compared with BP intervention only.

Although the difference in combined SBP/DBP goal attainment between the two treatment arms was not statistically significant in this study, a 4 mm Hg difference in SBP at week 6 was nevertheless observed, despite equal mean doses of amlodipine at week 6 in both treatment arms (data not shown). This may be due to a modest BP-lowering effect of the atorvastatin component of the single-pill combination which has previously been reported for statins.<sup>12,13</sup>

The participants in the TOGETHER trial consisted of previously treated hypertensive individuals with additional CV risk factors but conventionally normal lipid levels (fasting LDL-C: ≤170 mg/dL [4.4 mmol/L]), in which a statin (in the form of the atorvastatin component in the single-pill AML/ATO study medication) in addition to AML + TLC

resulted in improved combined BP/LDL-C goals compared with individuals on AML + TLC alone. Cholesterol lowering in addition to an antihypertensive regimen has been shown to translate into reduced CHD outcomes in a hypertensive population with normal lipid levels (nonfasting TC  $\leq$  251.4 mg/dL [ $\leq$  6.5 mmol/L]) in the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA),<sup>14</sup> indicating that a simultaneous multiple risk factor management strategy results in improved CHD outcomes.

The efficacy and safety of AML/ATO single-pill therapy has been demonstrated in another randomized trial, the Caduet in Untreated Subjects Population (CUSP) trial.<sup>11</sup> The CUSP results are highly consistent with our results. In CUSP, similar to TOGETHER, a significant difference in combined BP ( $<140/90$  mm Hg)/LDL-C ( $<100$  mg/dL) goal attainment was reported between a treatment arm receiving AML/ATO + TLC versus a control arm (AML/ATO + TLC, 47.6% versus placebo + TLC, 1.7%;  $P < 0.001$ ) within a short period of time (4 weeks in CUSP versus 6 weeks in TOGETHER).<sup>11</sup> This suggests that AML/ATO single-pill therapy, in addition to TLC, provides CV benefits in both treated and untreated hypertensive individuals within a short period of time.

The results from the TOGETHER trial show that the initiation of a multiple risk factor management strategy using AML/ATO single-pill therapy + TLC leads to improvements in CV risk burden compared with an approach using an AML + TLC-based regimen alone based on current guideline recommendations, in patients previously treated with amlodipine.

## Conclusions

AML/ATO single-pill therapy + TLC is more effective in achieving combined BP/LDL-C therapeutic targets than an AML + TLC-based regimen based on current guidelines in treated hypertensive patients with additional CV risk factors, highlighting the utility of a simultaneous treatment approach for the rapid reduction of CV risk burden. The single-pill combination was well tolerated in these patients, in line with previous reports.

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## Disclosures

Dr Grimm receives grants/research support from Pfizer and Novartis; acts as a consultant for Merck, Pfizer, and Novartis; and is on the Speakers Bureau for Pfizer, Merck-Schering Plough, and Novartis.

Dr Malik has no real or perceived conflicts of interest pertaining to this study.

Dr Yunis and Dr Sutradhar are employees of Pfizer Inc.

Dr Kursun was an employee of Pfizer Inc at the time the study was conducted.

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## Appendix

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