Changes in Cardiovascular Risk Associated With *Phentermine* and *Topiramate* Extended-Release in Participants With Comorbidities and a Body Mass Index ≥27 kg/m^2

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The aim of this analysis was to evaluate changes in cardiovascular risk factors in obese patients with dyslipidemia and/or hypertension receiving phentermine (PHEN) and topiramate extended-release (TPM ER). In the 56-week, randomized, double-blind, placebo-controlled, multicenter CONQUER trial, PHEN/TPM ER demonstrated significant weight loss compared with placebo in overweight or obese participants with ≥2 weight-related co-morbidities. Participants with body mass indexes of 27 to 45 kg/m^2 were randomized to placebo, PHEN 7.5 mg/TPM ER 46 mg, or PHEN 15 mg/TPM ER 92 mg; participants also received lifestyle modification counseling. Primary end points were percentage weight loss and the proportion of participants achieving ≥5% weight loss. Additional end points were changes in lipid variables in the dyslipidemia population and blood pressure in the hypertensive population, stratified by treatment and magnitude of weight loss. PHEN/TPM ER produced significantly greater dose-related mean percentage weight loss compared with placebo in the subgroups of participants with dyslipidemia and those with hypertension. Regardless of treatment group assignment, participants with dyslipidemia who lost ≥5% of their baseline weight experienced significantly greater reductions in triglycerides (−14.5% to −39.8%), and in non–high-density lipoprotein cholesterol (−9.4% to −14.8%) than those losing <5% of their weight ($p < 0.05$). Similarly, participants with hypertension at baseline showed reduced systolic blood pressure by −7.5 to −11.8 mm Hg ($p < 0.001$ vs those with <5% weight loss). In conclusion, the dose-related weight loss induced by PHEN/TPM ER treatment was accompanied by significant improvements in cardiovascular disease risk factors in participants who had dyslipidemia or hypertension at baseline, suggesting that facilitating weight loss by augmenting lifestyle changes with pharmacotherapies may decrease the risk for cardiovascular disease in obese and overweight patients with co-morbidities.

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Pharmacotherapy with phentermine (PHEN) and topiramate extended-release (TPM ER) has been shown to reduce weight in obese patients and was approved in 2012 as an adjunct to a reduced-calorie diet and increased physical activity for long-term weight management in adult patients with initial body mass indexes ≥30 kg/m^2 (obese) or ≥27 kg/m^2 (overweight) in the presence of ≥1 weight-related co-morbidity.[1–4] The combination therapy includes PHEN hydrochloride, a centrally acting appetite suppressant, approved by the US Food and Drug Administration for the short-term (a few weeks; up to 37.5 mg/day) treatment of obesity,[5,6] and TPM, a centrally acting agent approved in immediate-release formulation for the treatment of epilepsy and the prevention of migraine headaches.[7] This combination has been shown to result in weight loss and improvements in lipids, glycemic variables, and blood pressure in obese patients in randomized studies, but it is not approved by the Food and Drug Administration for weight reduction.[8–10] The 56-week phase 3 CONQUER study demonstrated that the administration of the once-daily, extended-release combination of PHEN/TPM ER as an adjunct to lifestyle intervention had good tolerability and was effective in reducing weight and improving cardiometabolic risk factors in overweight and obese patients with ≥2 weight-related co-morbidities.[2] In the present subanalysis, we evaluated changes in cardiovascular disease risk factors in subgroups of participants with dyslipidemia and/or hypertension at the start of the study.

Methods

The design and main results of the study have been published previously.[2] Briefly, CONQUER was a 56-week, randomized, double-blind, placebo-controlled, multicenter (93 United States sites) study that evaluated weight loss in overweight and obese participants with multiple weight-related co-morbidities who were treated with PHEN/TPM ER as an adjunct to lifestyle modification. The trial was approved by each site's institutional review board, and all participants

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Table 1
Baseline characteristics

Variable	Overall Population		Subgroup With Dyslipidemia		Subgroup With Hypertension	
	N	Value	n	Value	n	Value
Age (yrs)	2,487	51.1 ± 10.4	1,341	50.7 ± 10.5	1,305	53.0 ± 9.8
Women	2,487	1,737 (69.8%)	1,341	867 (64.7%)	1,305	860 (65.9%)
White	2,487	2,140 (86.0%)	1,341	1,240 (92.5%)	1,305	1,087 (83.3%)
Black	2,487	292 (11.7%)	1,341	64 (4.8%)	1,305	191 (14.6%)
Hispanic or Latino	2,487	328 (13.2%)	1,341	184 (13.7%)	1,305	132 (10.1%)
Not Hispanic or Latino	2,487	2,159 (86.8%)	1,341	1,157 (86.3%)	1,305	1,173 (89.9%)
Weight (kg)	2,485	103.1 ± 17.9	1,341	103.7 ± 18.1	1,305	104.4 ± 18.4
Body mass index (kg/m^2)	2,485	36.6 ± 4.5	1,341	36.5 ± 4.5	1,305	36.7 ± 4.6
Waist circumference (cm)	2,485	113.2 ± 12.3	1,341	113.7 ± 12.0	1,305	114.0 ± 12.6
Blood pressure (mm Hg)						
Systolic	2,485	128.4 ± 13.5	1,341	127.6 ± 13.4	1,305	134.2 ± 13.0
Diastolic	2,485	80.6 ± 9.1	1,341	80.4 ± 9.1	1,305	83.7 ± 9.1
Heart rate (beats/min)	2,485	72.3 ± 10.0	1,341	72.8 ± 10.3	1,305	71.6 ± 10.4
Non-HDL cholesterol (mg/dl)	2,485	155.6 ± 39.7	1,341	166.7 ± 40.7	1,305	153.8 ± 39.1
LDL cholesterol (mg/dl)	2,480	123.1 ± 35.4	1,336	124.3 ± 37.7	1,303	123.0 ± 35.7
HDL cholesterol (mg/dl)	2,485	48.9 ± 13.6	1,341	44.4 ± 11.4	1,305	49.6 ± 13.7
Triglycerides (mg/dl)	2,485	162.5 ± 74.1	1,341	212.5 ± 64.0	1,305	154.0 ± 68.3
Fasting glucose (mg/dl)	2,476	106.1 ± 22.2	1,335	107.4 ± 23.4	1,301	105.6 ± 20.7
Glycosylated hemoglobin (%)	2,478	5.9 ± 0.8	1,339	5.9 ± 0.8	1,302	5.9 ± 0.7
Fasting insulin (μIU/ml)	2,467	18.1 ± 15.1	1,335	19.8 ± 14.8	1,295	18.4 ± 15.2
High-sensitivity C-reactive protein (mg/L)	2,473	6.6 ± 10.1	1,337	6.6 ± 11.5	1,297	6.5 ± 11.4
Adiponectin (μg/mL)	2,001	8.0 ± 4.6	1,066	7.1 ± 3.9	1,058	8.1 ± 4.7
Fibrinogen (mg/dl)	2,479	457.4 ± 92.4	1,340	448.9 ± 90.7	1,301	458.5 ± 92.0
10-year Framingham score	1,887	4.8 ± 5.7	1,024	5.6 ± 6.3	1,004	5.8 ± 6.1
10-year Reynolds risk score	2,051	5.9 ± 6.2	1,112	6.5 ± 6.5	1,068	7.2 ± 6.9

Data are expressed as mean ± SD or as number (percentage).
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

provided written informed consent. The study was conducted from November 1, 2007 to June 30, 2009. This trial is registered with ClinicalTrials.gov (NCT00553787).

Participants were eligible to enroll in the study if they had body mass indexes of 27 to 45 kg/m^2, were 18 to 70 years of age, and had ≥2 weight-related co-morbidities.[2] Hypertension was defined as systolic blood pressure ≥140 and ≤160 mm Hg (or ≥130 and ≤160 mm Hg if diabetic), diastolic blood pressure ≥90 and ≤100 mm Hg (or ≥85 and ≤100 mm Hg if diabetic), or the use of ≥2 antihypertensive medications. Although the study protocol defined dyslipidemia as triglycerides ≥200 and ≤400 mg/dl (or using ≥2 lipid-lowering medications), for the purposes of this subgroup evaluation, analyses were performed using a lower triglyceride threshold (≥150 mg/dl) on the basis of established criteria.[11] Detailed inclusion and exclusion criteria for this study have been described previously.[2]

After a 2-week screening period, eligible participants were randomly assigned in a 2:1:2 ratio to receive blinded, once-daily treatment with placebo, PHEN 7.5 mg/TPM ER 46 mg (7.5/46), or PHEN 15 mg/TPM ER 92 mg (15/92). They then underwent a blinded 4-week titration period and were maintained for 52 weeks at the randomized dose.[2] Randomization was stratified by gender and diabetic status. All participants received standardized diet and lifestyle modification counseling at each study visit, including a 500 kcal/day reduction in caloric intake, on the basis of the LEARN (Lifestyle, Exercise, Attitudes, Relationships, Nutrition) program.[12] Co-morbidities were actively managed according to national guidelines, including the careful monitoring and adjustment of concomitant medications.

Predefined end points in the overall population were mean percentage weight loss and the proportion of participants achieving ≥5% weight loss. In this post hoc analysis of subjects with dyslipidemia, mean percentage weight loss, changes in lipid variables, concomitant lipid-lowering medications, and serum inflammatory biomarkers (adiponectin, fibrinogen, and high-sensitivity C-reactive protein) were evaluated. In the post hoc analysis of subjects with hypertension, mean percentage weight loss, changes in blood pressure, achievement of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommended blood pressure goal of <140/90 mm Hg (or <130/80 mm Hg in patients with type 2 diabetes mellitus),[13] and concomitant antihypertensive medication use were assessed. All additional end points were also stratified by degree of weight loss (<5%, ≥5% to <10%, ≥10% to <15%, and ≥15%). Safety assessments included physical examination, incidence of adverse events, changes in laboratory safety parameters, vital signs including heart rate, and electrocardiographic parameters (RR interval, QRS duration, and QT interval).[2] Subjects with clinically significant abnormal electrocardiographic findings at baseline were excluded from the study.

Statistical analyses of the coprimary and other efficacy end points were described previously.[2] Analysis-of-covariance and analysis-of-variance models were used to determine if there were residual effects of drug treatment on lipid

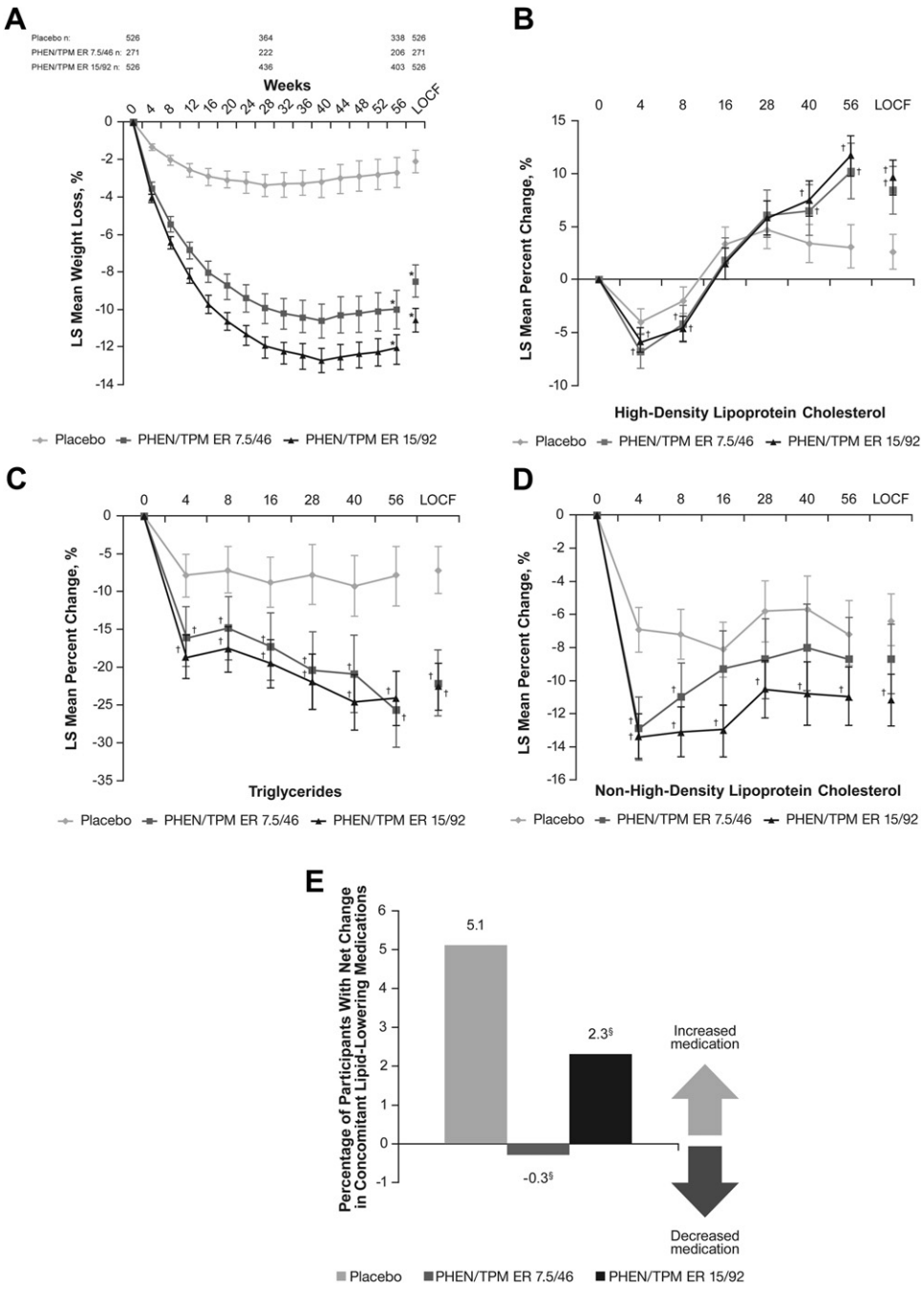

Figure 1. Effects of PHEN/TPM ER treatment on lipid variables and lipid-lowering medication use in the dyslipidemia subgroup. Least squares (LS) mean percentage changes from baseline to week 56 in *(A)* weight, *(B)* high-density lipoprotein cholesterol (HDL-C), *(C)* triglycerides, and *(D)* non-HDL-C and *(E)* net change (percentage increase minus percentage decrease) in concomitant lipid-lowering medications. *p <0.0001 versus placebo; †p <0.05 versus placebo; §p = 0.1803 for between-group comparisons. LOCF = last observation carried forward.

parameters and blood pressure after adjusting for weight loss. The percentages of subjects achieving categorical weight loss ≥5%, ≥10%, and ≥15% were compared among treatment groups using the chi-square test.

Results

Of the overall randomized population (N = 2,487), 1,341 participants (53.9%) met criteria for dyslipidemia, 1,305 participants (52.5%) had hypertension, and 393 (15.8%) had type 2 diabetes mellitus at baseline. Of the randomized population, 18.5% (459 of 2,487) had triglycerides <150 mg/dl but had high-density lipoprotein cholesterol <40 to 50 mg/dl and low-density lipoprotein cholesterol >160 mg/dl. These participants were not considered as meeting criteria for dyslipidemia in the present analysis. In total, 647 subjects (26.0%) had dyslipidemia and hypertension at baseline and were included in the 2 subgroup analyses. Some differences in baseline characteristics were seen between the overall sample and the

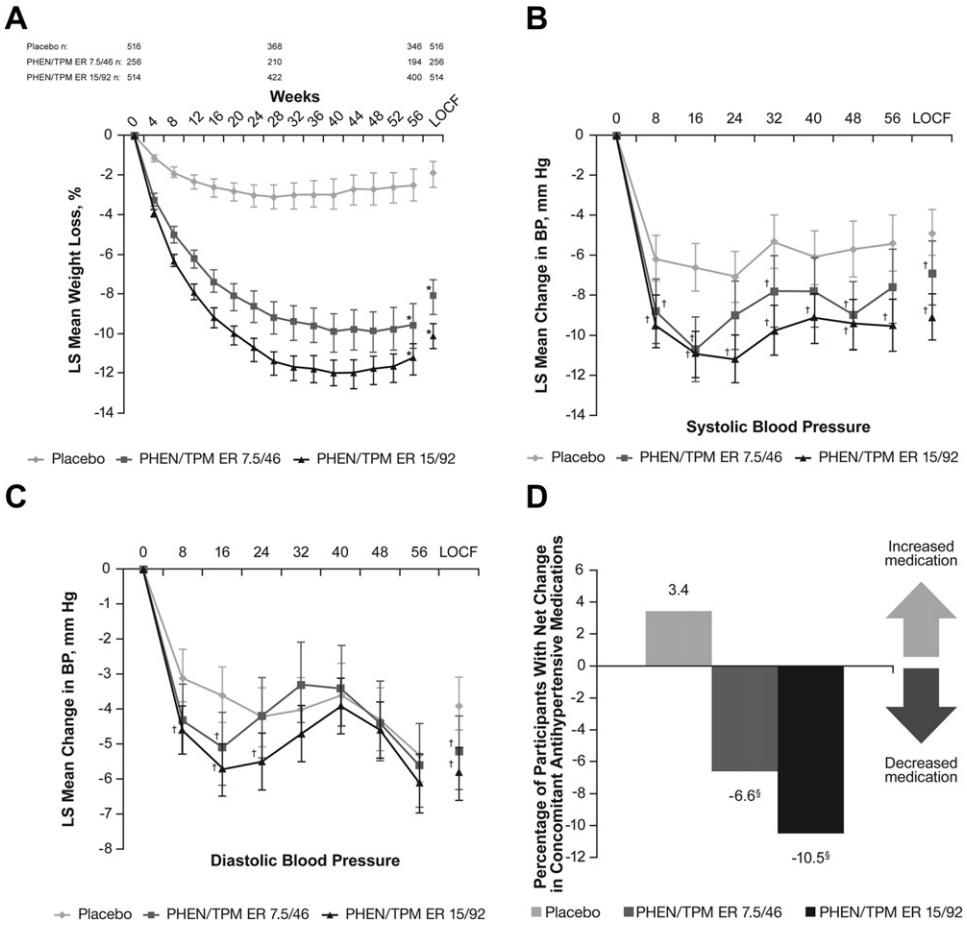

Figure 2. Effects of PHEN/TPM ER treatment on blood pressure (BP) and antihypertensive medications in the hypertensive subgroup. Least squares (LS) mean percentage changes from baseline to week 56 in *(A)* weight, *(B)* systolic BP, and *(C)* diastolic BP and *(D)* net change (percentage increase minus percentage decrease) in concomitant antihypertensive medication use. *p <0.0001 versus placebo; †p <0.05 versus placebo; §p <0.0001 for between-group comparisons. LOCF = last observation carried forward.

subgroups of participants in the present analyses in blood pressure, lipid profile, gender, and ethnicity (Table 1).

However, other baseline characteristics were similar across treatment groups in each of these populations (data not shown). In total, 147 participants (6.0%) in the overall population had histories of cardiac disorders, including histories of myocardial infarction (37 [1.5%]), coronary artery disease (26 [1.1%]), arrhythmia (10 [0.4%]), angina pectoris (7 [0.3%]), unstable angina (2 [0.1%]), and heart failure (3 [0.1%]).

The most common classes of lipid-controlling medications used at baseline in participants with dyslipidemia were statins (28.9%), fibrates (5.9%), nicotinic acid and its derivatives (3.5%), and bile-acid sequestrants (1.1%). The most common antihypertensive medications used in participants with hypertension at baseline were angiotensin-converting enzyme inhibitors alone (26.9%) or in combination with diuretics (5.8%) or calcium channel blockers (3.5%), β blockers alone (24.1%), and angiotensin II antagonists alone (15.5%) or in combination with diuretics (12.4%) or calcium channel blockers (0.9%). Twenty-nine participants (2.4%) with dyslipidemia at baseline and 38 (3.0%) with hypertension at baseline were taking aspirin at the beginning of the study.

Compared with placebo, PHEN/TPM ER produced significantly greater least squares mean percentage weight loss in the subgroup with dyslipidemia at baseline (−2.1%, −8.5%, and −10.5% for placebo, 7.5/46, and 15/92, respectively, p <0.0001; Figure 1) and in those with hypertension at baseline (−1.9%, −8.1%, and −10.1% for placebo, 7.5/46, and 15/92, respectively, p <0.0001; Figure 2). In addition, significantly more participants receiving PHEN/TPM ER achieved weight loss of ≥5%, ≥10%, and ≥15% compared with those receiving placebo in the subgroup with dyslipidemia and in the subgroup with hypertension (Supplemental Table 1).

Similar to the overall population,[2] among participants with dyslipidemia, there were significant improvements with PHEN/TPM ER versus placebo in serum high-density lipoprotein cholesterol and triglyceride levels (Figure 1). In this subanalysis, significant improvements were also seen in non−high-density lipoprotein cholesterol (Figure 1). Importantly, improvements in these lipid variables were greater with increasing degrees of weight loss, as were improvements in inflammatory biomarkers (Table 2). No clinically meaningful or statistically significant differences among treatment groups were observed in lipid parameters after adjusting for degree of weight loss (data not shown). A trend toward a net reduction in the percentage of participants using lipid-lowering medications was also seen in the

Table 2
Effects of weight loss on cardiometabolic parameters stratified by magnitude of weight loss for subjects with dyslipidemia at baseline

Variable	n	<5% Weight Loss	n	≥5% to <10% Weight Loss	n	≥10% to <15% Weight Loss	n	≥15% Weight Loss
Non-HDL cholesterol	617	−5.8% (−7.2% to −4.4%)	267	−9.4% (−11.5% to −7.3%)*	178	−10.7% (−13.3% to −8.2%)*	217	−14.8% (−17.1% to −12.5%)†,‡
LDL cholesterol	609	−4.6% (−6.5% to −2.7%)	267	−4.8% (−7.7% to −1.9%)	178	−3.2% (−6.8% to 0.3%)	217	−2.3% (−5.5% to 0.9%)
HDL cholesterol	617	1.7% (0.4% to 3.1%)	267	4.7% (2.6% to 6.7%)*	178	10.8% (8.3% to 13.4%)†,‡	217	19.7% (17.4% to 22.0%)†,§
Triglycerides	617	−5.5% (−8.2% to −2.8%)	267	−14.5% (−18.6% to −10.4%)*	178	−28.7% (−33.7% to −23.7%)†,§	217	−39.8% (−44.3% to −35.3%)†,§
High-sensitivity C-reactive protein (mg/L)	464	−1.1 (−1.7 to −0.5)	228	−2.1 (−3.0 to −1.2)	164	−3.1 (−4.2 to −2.0)*	206	−3.1 (−4.0 to −2.1)*
Adiponectin (μg/ml)	462	0.2 (0.0 to 0.4)	227	1.1 (0.8 to 1.4)†	161	1.8 (1.4 to 2.1)†,‡	209	3.6 (3.3 to 3.9)†,§
Fibrinogen (mg/dl)	462	−6.6 (−13.7 to 0.5)	227	−1.2 (−11.2 to 8.9)	163	−4.6 (−16.5 to 7.4)	208	−13.6 (−24.2 to −3.1)

Values in parentheses are 95% confidence intervals.
Abbreviations as in Table 1.
* $p < 0.05$ versus <5% weight loss.
† $p < 0.0001$ versus <5% weight loss.
‡ $p < 0.05$ versus ≥5% to <10% weight loss.
§ $p < 0.0001$ versus ≥5% to <10% weight loss.

2 PHEN/TPM ER groups compared with the placebo group ($p = 0.1803$ for between-group comparisons; Figure 1).

In line with the findings from the overall population,[2] there were greater reductions from baseline in systolic blood pressure and diastolic blood pressure in participants with hypertension receiving PHEN/TPM ER compared with placebo (Figure 2). Importantly, greater weight loss resulted in greater improvements in blood pressure, regardless of treatment group assignment (Table 3), with no significant differences between treatment groups in blood pressure reduction after adjusting for degree of weight loss (data not shown). However, no additional improvement was seen when weight loss was ≥15%.

Compared with placebo, a greater percentage of PHEN/TPM ER−treated participants with uncontrolled hypertension at baseline (≥140/90 mm Hg; placebo n = 104, 7.5/46 n = 40, and 15/92 n = 72) achieved the blood pressure goal of <140/90 mm Hg by week 56: 55 (52.9%) in the placebo group, 25 (62.5%) in the 7.5/46 group, and 54 (75.0%) in the 15/92 group ($p = 0.2996$ for 7.5/46 vs placebo, $p = 0.0034$ for 15/92 vs placebo). Furthermore, in 11 (10.6%), 4 (10.0%), and 13 (18.1%) participants with uncontrolled hypertension at baseline in the placebo, 7.5/46, and 15/92 groups, respectively, blood pressure was normalized to ≤120/80 mm Hg at 1 year. Use of concomitant antihypertensive drugs in participants with hypertension was reduced in PHEN/TPM ER−treated participants, but there was a net increase in the use of antihypertensive medications in the placebo group ($p < 0.0001$ for between-group comparisons; Figure 2).

The overall safety of treatment with PHEN/TPM ER in the entire population of the CONQUER trial was similar to that observed in the subgroups presented here.[2] Safety findings for the overall population have been described fully elsewhere.[2] In the subgroup with dyslipidemia, treatment-emergent adverse events occurred in 75.9%, 86.5%, and 88.3% of the placebo, 7.5/46, and 15/92 groups, respectively. In the subgroup with hypertension, the rates were 77.3%, 85.4%, and 88.8%, respectively. The most common treatment-emergent adverse events in the subgroup with dyslipidemia and the subgroup with hypertension were dry mouth, paresthesia, constipation, upper respiratory tract infection, and nasopharyngitis (Table 4). The rates of serious adverse events were similar among treatment groups (for placebo, 7.5/46, and 15/92, in the subgroup with dyslipidemia, 4.3%, 4.0%, and 3.8%, and in the subgroup with hypertension, 4.2%, 3.4%, and 3.7%, respectively). For the placebo, 7.5/46, and 15/92 groups, respectively, discontinuation because of adverse events occurred in 8.8%, 12.4%, and 18.0% in the subgroup with dyslipidemia and 9.7%, 11.9%, and 19.8% in the subgroup with hypertension. There was 1 death, occurring in the placebo group of the subgroup with dyslipidemia.

In total, 3.8% of participants in the subgroup with dyslipidemia experienced treatment-emergent adverse events in the cardiac disorders system-organ class (3.0%, 4.4%, and 4.3% in the placebo, 7.5/46, and 15/92 groups, respectively). Most were reported as mild or moderate, with only 8 (0.6%) adverse events reported as severe. The only cardiac treatment-emergent adverse event occurring in ≥1% of participants with dyslipidemia was palpitations (0.9%, 2.9%, and 2.1% in the placebo, 7.5/46, and 15/92 groups,

Table 3
Effects of weight loss on blood pressure stratified by magnitude of weight loss for subjects with hypertension at baseline

Variable	<5% Weight Loss (n = 657)	≥5% to <10% Weight Loss (n = 253)	≥10% to <15% Weight Loss (n = 177)	≥15% Weight Loss (n = 199)
Systolic blood pressure (mm Hg)	−4.2 (−5.2 to −3.2)	−7.5 (−9.2 to −5.9)*	−10.8 (−12.7 to −8.9)†,‡	−11.8 (−13.6 to −10.0)†,§
Diastolic blood pressure (mm Hg)	−3.1 (−3.7 to −2.4)	−5.9 (−7.0 to −4.9)†	−7.5 (−8.8 to −6.3)†	−7.4 (−8.6 to −6.2)†

Data are least squares mean changes (intent to treat, last observation carried forward) with 95% confidence intervals in parentheses.
* p = 0.0007 versus <5% weight loss.
† p <0.0001 versus 5% weight loss.
‡ p = 0.0116 versus ≥5% to <10% weight loss.
§ p = 0.0006 versus ≥5% to <10% weight loss.

Table 4
Most common treatment-emergent adverse events in the subgroups with dyslipidemia and hypertension

Adverse Event	Subgroup With Dyslipidemia (ITT)			Subgroup With Hypertension (ITT)		
	Placebo (n = 535)	PHEN 7.5 mg/TPM ER 46 mg (n = 274)	PHEN 15 mg/TPM ER 92 mg (n = 532)	Placebo (n = 524)	PHEN 7.5 mg/TPM ER 46 mg (n = 261)	PHEN 15 mg/TPM ER 92 mg (n = 520)
Dry mouth	1.1%	12.4%	21.6%	2.3%	14.2%	22.7%
Paresthesia	2.2%	13.5%	20.1%	2.3%	14.2%	22.3%
Constipation	5.0%	17.2%	16.5%	5.5%	15.7%	18.1%
Upper respiratory tract infection	13.1%	11.3%	12.8%	11.8%	12.6%	12.1%
Nasopharyngitis	9.0%	9.5%	10.2%	8.8%	10.3%	10.2%
Dysgeusia	1.1%	8.8%	9.6%	0.8%	7.7%	11.0%
Insomnia	5.4%	5.8%	9.2%	4.8%	5.7%	11.0%
Headache	8.0%	9.5%	9.2%	8.4%	5.0%	10.8%
Dizziness	3.2%	7.3%	9.6%	3.1%	6.5%	12.1%
Sinusitis	5.4%	8.4%	9.4%	6.5%	5.4%	8.3%

ITT = intent to treat.

respectively). Serious adverse cardiac events occurred in 11 participants (0.8%) with dyslipidemia, and serious adverse vascular events occurred in 1 participant (0.1%) with dyslipidemia. One participant with dyslipidemia in the placebo group died from cardiopulmonary arrest (considered unrelated to the study drug).

In total, 2.6% of participants with hypertension experienced treatment-emergent adverse events in the cardiac disorders system-organ class (1.7%, 2.3%, and 3.7% in the placebo, 7.5/46, and 15/92 groups, respectively). Most were reported as mild or moderate, with only 5 adverse events (0.4%) reported as severe. The only cardiac treatment-emergent adverse event occurring in ≥1% of participants with hypertension was palpitations (0.6%, 0.8%, and 1.2% in the placebo, 7.5/46, and 15/92 groups, respectively). Serious adverse cardiac events occurred in 6 participants (0.5%) with hypertension, and serious adverse vascular events occurred in 2 participants (0.2%) with hypertension.

Rates of serious adverse cardiac and vascular events in the overall population were similar to those seen in the subgroups (Supplemental Table 2). Mean changes in heart rate from baseline to week 56 in the safety analysis were −0.5 ± 10.2 beats/min (range −51 to 40), 0.1 ± 10.8 beats/min (range −42 to 34), and 1.3 ± 10.3 beats/min (range −34 to 33) for the placebo, 7.5/46, and 15/92 groups, respectively, in the subgroup with dyslipidemia and 0.2 ± 10.1 beats/min (range −51 to 40), 1.0 ± 10.1 beats/min (range −42 to 38), and 0.8 ± 10.4 beats/min (range −31 to 33) for the placebo, 7.5/46, and 15/92 groups, respectively, in the subgroup with hypertension. Clinically significant electrocardiographic abnormalities according to investigator discretion were observed in 1.0%, 0.4%, and 0.4% of those in the placebo, 7.5/46, and 15/92 groups, respectively, in the subgroup with dyslipidemia and 1.7%, 1.4%, and 0.2% of those in the placebo, 7.5/46, and 15/92 groups, respectively, in the subgroup with hypertension. No other investigator-reported clinically important differences in mean changes in electrocardiographic parameters were seen among the treatment groups in either subgroup (Supplemental Table 3).

In the placebo, 7.5/46, and 15/92 groups, respectively, hypokalemia was noted in 2 (0.4%), 6 (2.2%), and 9 (1.7%) participants in the subgroup with dyslipidemia and 3 (0.6%), 5 (1.9%), and 26 (5.0%) participants in the subgroup with hypertension. Persistence of potassium concentrations lower than the lower limit of normal (<3.5 mmol/L at 2 consecutive visits or at study exit) was seen in 6 (1.1%), 10 (3.7%), and 25 (4.7%) participants in the subgroup with dyslipidemia and 9 (1.7%), 15 (5.8%), and 40 (7.7%) participants in the subgroup with hypertension. None of the cases of hypokalemia was rated as severe, and percentages of participants receiving potassium supplementation at any point during the course of the study were comparable among groups (2.8% to 4.7% in the subgroup with dyslipidemia and 5.4% to 8.3% in the subgroup with hypertension).[2] In the placebo, 7.5/46, and 15/92 groups, respectively, persistence of low bicarbonate concentrations (<21 mmol/L at 2 consecutive visits or at study exit) was seen in 10 (1.9%), 18 (6.6%), and 48 (9.0%) participants in the subgroup with dyslipidemia and in 11

(2.1%), 10 (3.8%), and 33 (6.4%) participants in the subgroup with hypertension. One (0.2%) and 4 (0.8%) participants with dyslipidemia and 1 (0.2%) and 2 (0.4%) participants with hypertension in the placebo and 15/92 groups, respectively, had persistently low bicarbonate concentrations <17 mmol/L. In the 15/92 group, 1 participant (0.1%) with hypertension and 1 participant (0.2%) with dyslipidemia showed a mild increase in serum chloride level. Serum sodium showed a mild decrease in 1 participant (0.2%) with dyslipidemia in the 15/92 group. One (0.2%) placebo and 6 (1.1%) 15/92 participants with dyslipidemia (not significant vs placebo) and 1 (0.2%) placebo and 9 (1.7%) 15/92 participants with hypertension ($p = 0.0053$ vs placebo) had nephrolithiasis. Mild metabolic acidosis was found as a treatment-emergent adverse event in 1 participant (0.4%) with hypertension in the 7.5/46 group; no metabolic acidosis events were observed in the dyslipidemia population.

Discussion

Treatment with PHEN/TPM ER has been shown to be effective in promoting significant weight loss in a dose-related fashion compared with placebo over 56 weeks when used in conjunction with lifestyle intervention.[2] This subgroup analysis of participants who had dyslipidemia or hypertension at baseline supports and extends this previous finding, demonstrating that compared with placebo, PHEN/TPM ER treatment leads to significant weight loss accompanied by significant improvements in cardiovascular risk factors, including blood pressure, lipid, and inflammatory biomarker levels, as well as reductions in medication use. Importantly, this study also demonstrated that increasing degrees of weight loss up to 10% to 15% were associated with greater improvements in cardiovascular risk factors. These findings demonstrate the potential benefit of adding pharmacotherapy to a weight-loss program that incorporates lifestyle changes in the overall management of obese and overweight patients with associated cardiometabolic conditions.

A positive relation between degree of weight loss and magnitude of improvements in cardiovascular risk factors has been previously demonstrated,[14–16] while another study has shown that differences in improvements in total and low-density lipoprotein cholesterol were related to the amount of weight lost and successfully maintained over the long term (2 years).[17] Specifically, in the Action for Health in Diabetes (Look AHEAD) study, which assessed the impact of lifestyle interventions resulting in modest weight loss on cardiovascular risk factors in patients with type 2 diabetes, weight loss of ≥2% to <5% was associated with improvements in some but not all risk factors measured, weight loss of ≥5% to <10% led to significant improvements in all risk factors, and greater weight loss (≥10% to <15%, and ≥15%) was associated with significant and increasing improvements in all cardiovascular risk factors except low-density lipoprotein cholesterol.[16] It is noteworthy that only a small proportion of subjects in the Look AHEAD study (<1% of the total population studied) lost ≥15% body weight when using lifestyle interventions.[16] In the present study, participants showed incremental improvements in cardiovascular risk factors with up to 10% to 15% weight loss, but those with weight loss ≥15% did not significantly differ compared with those who lost ≥10% to <15% of their body weight. However, it is difficult to draw any substantive conclusions, because the population was relatively well controlled at baseline, and those who lost ≥10% to <15% of their body weight were within the normotensive range at the end point, so additional incremental and significant improvements would be difficult to demonstrate in a study of this size and in this population.

Overall, changes in serum lipid levels associated with PHEN/TPM ER use in participants with dyslipidemia at baseline suggest that lipid parameters can be markedly affected by weight loss.[9,18] The reductions in non–high-density lipoprotein cholesterol of approximately 10% to 15% associated with PHEN/TPM ER–induced weight loss of ≥5% in patients already managed to standard of care were comparable with the effect of fibrate therapy for combined dyslipidemia.[19] It appears that weight loss associated with PHEN/TPM ER treatment confers approximately a 5% to 20% increase in high-density lipoprotein cholesterol, depending on the degree of weight loss, suggesting that PHEN/TPM ER is a promising option for the treatment of overweight and obese patients with an atherogenic dyslipidemic profile. Although not statistically significant, it should be noted that these improvements were seen despite a net numeric reduction in the use of lipid-lowering medications over 56 weeks in participants receiving PHEN/TPM ER compared with those receiving placebo.

Of the participants with hypertension managed to standard of care at baseline, reductions in blood pressure were observed along with significant weight loss. The reduction in blood pressure also occurred despite a net reduction in the use of antihypertensive medications in PHEN/TPM ER–treated participants. Furthermore, a greater proportion of participants receiving PHEN/TPM ER with uncontrolled hypertension (≥140/90 mm Hg) at baseline achieved blood pressure control (<140/90 mm Hg) compared with those receiving placebo, and 10% to 18% of participants receiving PHEN/TPM ER and 11% of participants receiving placebo normalized their blood pressure (≤120/80 mm Hg). This finding is potentially significant, because only half of the United States population with hypertension is able to achieve adequate blood pressure control.[20] In addition, such reductions in medication burden are important, given that multiple medications are often required by patients with hypertension to achieve control.[21]

In line with the findings from the overall CONQUER population,[2] PHEN/TPM ER treatment was well tolerated in participants who had hypertension or dyslipidemia at baseline, with dry mouth, constipation, and paresthesia being the most common adverse events. There was a dose-related increase in discontinuation rates due to adverse events, although discontinuations were infrequent overall (12% to 20% for PHEN/TPM ER participants). In contrast with the propensity of sympathomimetic weight-loss drugs (e.g., sibutramine) to increase blood pressure and heart rate,[22] PHEN/TPM ER weight loss was associated with a consistent decrease in blood pressure, despite a small increase in heart rate (0.1 to 1.3 beats/minute). Cardiac adverse events were infrequent during the study for all treatment groups.

In the present study, PHEN/TPM ER treatment was associated with more nonsevere hypokalemia and low

bicarbonate concentrations than lifestyle intervention alone, but potassium supplementation across the study was comparable among groups, and mild metabolic acidosis was found in only 1 study participant.

This subanalysis had limitations. Primarily, the main study included a broad population of obese participants and, as such, was not powered to address outcomes related to particular cardiovascular disease risk factors. However, although the population in each co-morbidity subset was approximately half the total study population, efficacy and safety results were comparable with those in the overall population.

Taken together, the dose-related weight loss induced by PHEN/TPM ER, the associated beneficial effects on cardiometabolic risk factors, and the reductions in medication use indicate that PHEN/TPM ER treatment may be an important addition to the therapeutic armamentarium for obese and overweight patients with co-morbidities such as hypertension and dyslipidemia.

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Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.amjcard.2012.12.038.

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