ORIGINAL ARTICLE

Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients

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ABSTRACT

BACKGROUND

Lorcaserin, a selective serotonin 2C receptor agonist that modulates appetite, has proven efficacy for weight management in overweight or obese patients. The cardiovascular safety and efficacy of lorcaserin are undefined.

METHODS

We randomly assigned 12,000 overweight or obese patients with atherosclerotic cardiovascular disease or multiple cardiovascular risk factors to receive either lorcaserin (10 mg twice daily) or placebo. The primary safety outcome of major cardiovascular events (a composite of cardiovascular death, myocardial infarction, or stroke) was assessed at an interim analysis to exclude a noninferiority boundary of 1.4. If noninferiority was met, the primary cardiovascular efficacy outcome (a composite of major cardiovascular events, heart failure, hospitalization for unstable angina, or coronary revascularization [extended major cardiovascular events]) was assessed for superiority at the end of the trial.

RESULTS

At 1 year, weight loss of at least 5% had occurred in 1986 of 5135 patients (38.7%) in the lorcaserin group and in 883 of 5083 (17.4%) in the placebo group (odds ratio, 3.01; 95% confidence interval [CI], 2.74 to 3.30; P<0.001). Patients in the lorcaserin group had slightly better values with respect to cardiac risk factors (including blood pressure, heart rate, glycemic control, and lipids) than those in the placebo group. During a median follow-up of 3.3 years, the rate of the primary safety outcome was 2.0% per year in the lorcaserin group and 2.1% per year in the placebo group (hazard ratio, 0.99; 95% CI, 0.85 to 1.14; P<0.001 for noninferiority); the rate of extended major cardiovascular events was 4.1% per year and 4.2% per year, respectively (hazard ratio, 0.97; 95% CI, 0.87 to 1.07; P=0.55). Adverse events of special interest were uncommon, and the rates were generally similar in the two groups, except for a higher number of patients with serious hypoglycemia in the lorcaserin group (13 vs. 4, P=0.04).

CONCLUSIONS

In a high-risk population of overweight or obese patients, lorcaserin facilitated sustained weight loss without a higher rate of major cardiovascular events than that with placebo. (Funded by Eisai; CAMELLIA–TIMI 61 ClinicalTrials.gov number, NCT02019264.)

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*A complete list of the CAMELLIA–TIMI 61 steering committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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The prevalence of obesity has nearly tripled during the past 40 years worldwide.[1] As of 2016, 13% of adults globally were obese, with rates as high as 40% in several countries, including the United States.[1-3] (Obesity is defined as a body-mass index [BMI, the weight in kilograms divided by the square of the height in meters] of ≥30.) An additional 39% of adults worldwide are overweight (BMI, 25 to 29).[1] Obesity is associated with the development and progression of multiple coexisting complications, including hypertension, dyslipidemia, type 2 diabetes, coronary artery disease, stroke, and heart failure, as well as a risk of death from any cause.[4-6]

Weight-loss guidelines recommend the use of pharmacologic agents as adjuncts to lifestyle modification for long-term weight management in some patients.[6,7] However, no pharmacologic strategy has yet shown cardiovascular safety or benefit. Indeed, several agents have precipitated various cardiovascular or neuropsychiatric complications, which has led to their removal from markets by regulatory agencies and left clinicians without a pharmacologic weight-loss agent with proven cardiovascular safety.[8-10]

Lorcaserin is a selective agonist of the 5-hydroxytryptamine 2C serotonin receptor (5-HT2C), which regulates appetite through hypothalamic activation of the anorexigenic proopiomelanocortin (POMC) pathway.[11] On the basis of findings in weight-loss trials, lorcaserin was approved by the Food and Drug Administration (FDA) as an adjunct to a reduced-calorie diet and increased physical activity for long-term weight management.[12-14] In the CAMELLIA–TIMI 61 (Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients–Thrombolysis in Myocardial Infarction 61) trial, we investigated the long-term cardiovascular and metabolic safety and efficacy of lorcaserin in obese or overweight patients with established atherosclerotic cardiovascular disease or multiple cardiovascular risk factors.

Methods

Trial Design and Oversight

CAMELLIA–TIMI 61 was a randomized, double-blind, placebo-controlled, multinational clinical trial in which patients at 473 sites in eight countries underwent randomization. The trial was designed by the TIMI Study Group in conjunction with the executive committee and the trial sponsor and funder, Eisai.[15] The protocol and its amendments (available with the full text of this article at NEJM.org) were approved by the relevant ethics committee at each participating site. The sponsor was responsible for data collection. The raw database was provided to the TIMI Study Group, which conducted all the analyses for this report. The first author wrote the initial draft of the manuscript, and all the coauthors participated in subsequent revisions. The authors from the TIMI Study Group assume responsibility for the accuracy and completeness of the data and all the analyses, as well as for the fidelity of the trial to the protocol. We encourage parties interested in collaboration and data sharing to contact the corresponding author directly.

Population

Eligible patients were obese or overweight with a BMI of at least 27, along with either established atherosclerotic cardiovascular disease or multiple cardiovascular risk factors.[15] Full eligibility criteria and definitions are provided in the Supplementary Appendix, available at NEJM.org. Written informed consent was obtained from all the patients.

Trial Procedures

Eligible patients were randomly assigned in a 1:1 ratio to receive either lorcaserin (10 mg twice daily) or placebo in a blinded fashion until the end of the follow-up period. Randomization was stratified according to cardiovascular disease status (established cardiovascular disease or multiple cardiovascular risk factors only). Additional trial procedures are described in the Supplementary Appendix.[15]

All the patients were provided access to and were encouraged to participate in a standardized weight-management program, which consisted of intensive, multicomponent behavior therapy that included dietary and exercise information. Patients also had unlimited access to a registered dietitian by telephone.

We prespecified the conduct of an echocardiographic substudy involving at least 4000 patients, which would include the evaluation of the development or progression of pulmonary hypertension or FDA-defined valvulopathy, as seen on serial, centrally read echocardiography. FDA-defined valvulopathy is categorized as mild or worse aortic regurgitation or moderate or worse mitral regurgitation. (Details about the substudy are provided in the Supplementary Appendix.)

PRIMARY AND SECONDARY OUTCOMES

The primary safety outcome was major cardiovascular events (a composite of cardiovascular death, myocardial infarction, or stroke). The primary cardiovascular efficacy outcome was a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or any coronary revascularization (extended major cardiovascular events). New-onset diabetes in patients with prediabetes at baseline was a key secondary efficacy outcome. Other prespecified safety outcomes and their definitions are described in the Supplementary Appendix. A central clinical events adjudication committee, whose members were unaware of the trial-group assignments, adjudicated all primary and key secondary safety and efficacy outcomes.

STATISTICAL ANALYSIS

We used a two-step procedure in which the primary assessment was for cardiovascular safety, followed by an assessment of cardiovascular efficacy. The primary cardiovascular safety assessment for the noninferiority of lorcaserin versus placebo was conducted at an interim analysis after the prespecified number of events had accrued. If the criteria for noninferiority were met, the trial was to continue to assess for superiority of lorcaserin over placebo with respect to extended major cardiovascular events (i.e., including heart failure, hospitalization for unstable angina, or coronary revascularization) at the end of the trial.[15] We estimated that 460 primary safety outcome events would be required to provide a power of approximately 95% to rule out the FDA-defined noninferiority margin of 1.4 for lorcaserin versus placebo, using the upper boundary of the one-sided 97.5% confidence interval. We estimated that 1401 extended major cardiovascular events would be required to provide a power of at least 85% to detect a reduction of 15% in the relative risk of extended major cardiovascular events with lorcaserin as compared with placebo.

We performed all primary cardiovascular safety analyses and all efficacy analyses in the total population using the intention-to-treat method, with a sensitivity analysis that included events that had occurred while patients were receiving the assigned intervention. Other safety analyses were conducted in the safety population, which included patients who had received at least one dose of a trial agent and had undergone at least one post-dose safety assessment, and included events that had occurred during the intervention period. We calculated hazard ratios, 95% confidence intervals, and P values for time-to-event analyses using a Cox proportional-hazards model with the stratification factor as a covariate. Additional statistical procedures are described in the Supplementary Appendix.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From January 2014 through November 2015, a total of 12,000 patients underwent randomization. The median follow-up period was 3.3 years (interquartile range, 3.0 to 3.5). The patients' baseline characteristics were well balanced between the two groups (Table 1). Overall, the median age was 64 years, 64.2% of the patients were male, and the median BMI was 35. Patients had a high burden of coexisting conditions, including diabetes (in 56.8% of the patients), hypertension (90.4%), hyperlipidemia (93.6%), and chronic kidney disease (19.0%). A total of 8958 patients (74.7%) had established atherosclerotic cardiovascular disease. The baseline characteristics according to cardiovascular disease status are provided in Table S1 in the Supplementary Appendix.

The rate of premature discontinuation of a trial agent was 12.0% per year in the lorcaserin group (2248 of 6000 patients over a median of 3.3 years of follow-up) and 12.7% per year in the placebo group (2363 of 6000). The majority of premature discontinuations were due to patient choice unrelated to an adverse event (Table S2 in the Supplementary Appendix). The rate of withdrawal of consent was 0.6% per year (116 of 6000 patients) in the lorcaserin group and 0.7% per year (139 of 6000) in the placebo group; the rates of loss to follow-up were 0.2% per year (42 of 6000) and 0.3% per year (50 of 6000), respectively (Fig. S1 in the Supplementary Appendix). A final vital status was known for 97.4% of the patients.

EFFECT OF LORCASERIN ON WEIGHT

In a pooled analysis of the two trial groups, the median weight at baseline was 102.0 kg (interquartile range, 90.0 to 116.2). At 1 year, the least-squares mean change in weight from baseline was −4.2 kg in the lorcaserin group and −1.4 kg in the placebo group, for a between-group difference of 2.8 kg (P<0.001) (Fig. 1A). At 1 year, weight

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Lorcaserin (N = 6000)	Placebo (N = 6000)
Median age (IQR) — yr	64 (58–69)	64 (58–69)
Male sex — no. (%)	3888 (64.8)	3814 (63.6)
White race — no. (%)†	5309 (88.5)	5331 (88.9)
Median weight (IQR) — kg	102 (90–116)	102 (90–116)
Body-mass index‡		
Median (IQR)	35 (32–39)	35 (32–39)
Distribution — no. (%)		
<30	793 (13.2)	782 (13.0)
30 to <40	3866 (64.4)	3889 (64.8)
≥40	1341 (22.4)	1329 (22.2)
Region — no. (%)		
North America	4882 (81.4)	4910 (81.8)
Europe	498 (8.3)	487 (8.1)
Central or South America	182 (3.0)	190 (3.2)
Asia Pacific	438 (7.3)	413 (6.9)
Coexisting condition		
Hypertension — no. (%)	5414 (90.2)	5434 (90.6)
Hyperlipidemia — no. (%)	5616 (93.6)	5613 (93.6)
Estimated glomerular filtration rate <60 ml/min/1.73 m^2 — no./total no. (%)§	1149/5996 (19.2)	1208/5995 (20.2)
Urine albumin-to-creatinine ratio ≥30 mg/g — no./no. total (%)	1103/5988 (18.4)	1175/5993 (19.6)
High-sensitivity C-reactive protein >3 mg/liter — no./no. total (%)	2277/5985 (38.0)	2363/5982 (39.5)
Prediabetes — no. (%)¶	2015 (33.6)	1976 (32.9)
Diabetes — no. (%)¶	3385 (56.4)	3431 (57.2)
Cardiovascular condition		
Multiple cardiovascular risk factors — no. (%)	1512 (25.2)	1530 (25.5)
Established cardiovascular disease — no. (%)	4488 (74.8)	4470 (74.5)
Coronary artery disease — no. (%)	4096 (68.3)	4057 (67.6)
Myocardial infarction — no. (%)	2374 (39.6)	2398 (40.0)
Coronary revascularization — no. (%)	3661 (61.0)	3636 (60.6)
Peripheral artery disease — no./total no. (%)	339/5999 (5.7)	318/5997 (5.3)
Cerebrovascular disease — no. (%)	547 (9.1)	583 (9.7)
Medication — no. (%)		
Any serotonergic medication‖	1349 (22.5)	1377 (23.0)
Aspirin	4529 (75.5)	4518 (75.3)
Beta-blocker	3804 (63.4)	3741 (62.4)
ACE inhibitor or ARB	4477 (74.6)	4529 (75.5)
Statin	5123 (85.4)	5129 (85.5)
Ezetimibe	473 (7.9)	466 (7.8)

* There were no significant differences between the two groups in baseline characteristics. ACE denotes angiotensin-converting enzyme, ARB angiotensin II receptor blocker, and IQR interquartile range.
† Race was reported by the investigators.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The glomerular filtration rate was estimated by means of the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation.
¶ Definitions for glycemic subgroups are provided in the Supplementary Appendix.
‖ Classes of agents that are considered to be serotonergic according to the trial protocol are listed in the Supplementary Appendix.

loss of at least 5% had occurred in 1986 of 5135 patients (38.7%) in the lorcaserin group and in 883 of 5083 (17.4%) in the placebo group; weight loss of at least 10% had occurred in 748 of 5135 patients (14.6%) and in 243 of 5083 (4.8%), respectively (P<0.001 for both comparisons) (Fig. 1B).

Although the between-group difference in weight loss was largest at approximately 1 year, the difference remained significant through 40 months, with a change from baseline of −4.0 kg (95% confidence interval [CI], −4.3 to −3.8) with lorcaserin and −2.1 kg (95% CI, −2.3 to −1.8) with placebo, for a between-group difference of −1.9 kg (95% CI, −2.3 to −1.6; P<0.001). At 1 year, patients in the lorcaserin group had a greater reduction from baseline in BMI and waist circumference than those in the placebo group (Table S3 in the Supplementary Appendix).

EFFECT ON OTHER CARDIOVASCULAR RISK FACTORS

At 1 year, the rates of several cardiovascular and metabolic risk factors were slightly lower in the lorcaserin group than in the placebo group, including systolic blood pressure (between-group difference, −0.9 mm Hg), diastolic blood pressure (difference, −0.8 mm Hg), heart rate (difference, −1.0 beat per minute), low-density lipoprotein cholesterol (difference, −1.2 mg per deciliter [0.03 mmol per liter]), triglycerides (difference, −11.7 mg per deciliter [0.13 mmol per liter]), non–high-density lipoprotein cholesterol (difference, −2.6 mg per deciliter [0.07 mmol per liter]), and glycated hemoglobin (difference, −0.2% in the entire population; −0.3% in patients with diabetes at baseline) (Table S3 in the Supplementary Appendix). Among the patients who had prediabetes at baseline, new-onset diabetes was diagnosed in 172 of 2015 patients (8.5%, or 3.1% per year) in the lorcaserin group and in 204 of 1976 patients (10.3%, or 3.8% per year) in the placebo group (Table 2).

CARDIOVASCULAR SAFETY AND EFFICACY

At the time of trial completion, major cardiovascular events had occurred in 364 patients (6.1%, or 2.0% per year) in the lorcaserin group and 369 (6.2%, or 2.1% per year) in the placebo group (hazard ratio, 0.99; 95% CI, 0.85 to 1.14; P<0.001 for noninferiority) (Fig. 2A). Similar results were seen at the time of the interim analysis (Table 2) and at trial completion in the as-treated analysis (Table S4 in the Supplementary Appendix).

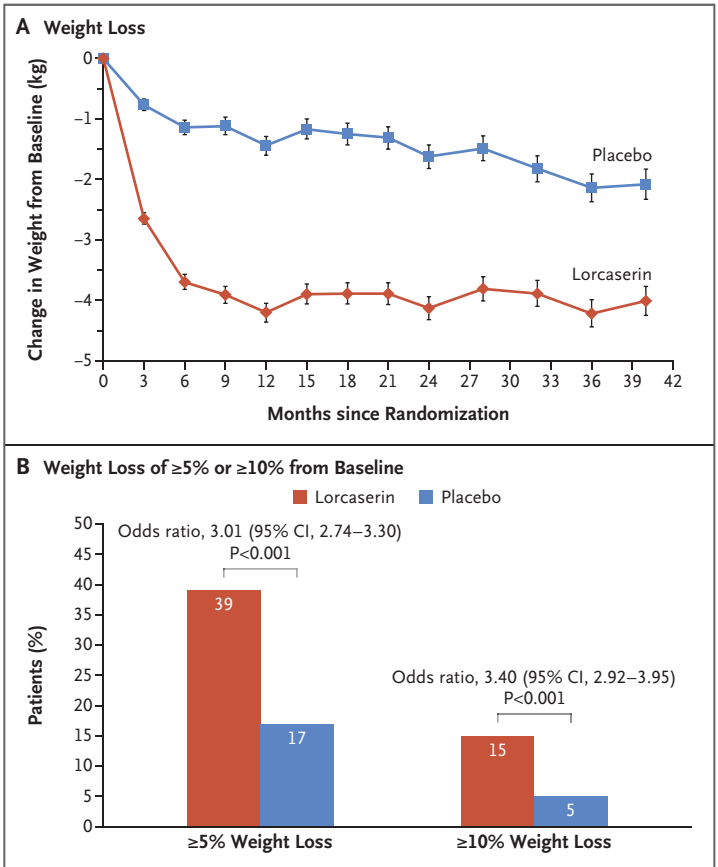

Figure 1. Weight Loss.

Panel A shows the change in weight from baseline (as least-squares means) among patients in the lorcaserin group and the placebo group. I bars indicate 95% confidence intervals. Panel B shows the percentage of patients with weight loss of at least 5% or at least 10% from baseline at 1 year in the lorcaserin group and the placebo group. The analyses included all the patients for whom data regarding weight were available at baseline and at 1 year (5135 patients in the lorcaserin group and 5083 in the placebo group).

The primary efficacy outcome of extended major cardiovascular events occurred in 707 patients (11.8%, or 4.1% per year) in the lorcaserin group and in 727 (12.1%, or 4.2% per year) in the placebo group (hazard ratio, 0.97; 95% CI, 0.87 to 1.07; P=0.55 for superiority) (Fig. 2B). Individual components of the composite outcome are shown in Table 2. The results were consistent with respect to cardiovascular safety and efficacy in prespecified subgroups (Figs. S3 and S4 in the Supplementary Appendix).

ADDITIONAL SAFETY ASSESSMENTS

No significant between-group differences were seen in the overall incidence of serious adverse

Table 2. Primary and Other Outcomes.*

Outcome	Lorcaserin (N=6000)		Placebo (N=6000)		Hazard Ratio (95% CI)
	no. of patients (%)	*annual rate (%)*	*no. of patients (%)*	*annual rate (%)*	
Primary safety outcome†					
Major cardiovascular event at interim analysis	242 (4.0)	NA	241 (4.0)	NA	1.01 (0.84–1.20)
Major cardiovascular event at trial completion	364 (6.1)	2.0	369 (6.2)	2.1	0.99 (0.85–1.14)
Primary cardiovascular efficacy outcome					
Extended major cardiovascular event‡	707 (11.8)	4.1	727 (12.1)	4.2	0.97 (0.87–1.07)
Cardiovascular death	90 (1.5)	0.5	86 (1.4)	0.5	1.04 (0.78–1.40)
Myocardial infarction	225 (3.8)	1.2	227 (3.8)	1.3	0.99 (0.82–1.19)
Stroke	84 (1.4)	0.5	98 (1.6)	0.5	0.86 (0.64–1.15)
Heart failure	143 (2.4)	0.8	150 (2.5)	0.8	0.95 (0.76–1.20)
Unstable angina	92 (1.5)	0.5	79 (1.3)	0.4	1.16 (0.86–1.57)
Coronary revascularization	408 (6.8)	2.3	414 (6.9)	2.3	0.98 (0.86–1.12)
Other outcomes					
Death from any cause	219 (3.7)	1.2	202 (3.4)	1.1	1.08 (0.89–1.31)
New-onset diabetes§	172 (8.5)	3.1	204 (10.3)	3.8	0.81 (0.66–0.99)

* The primary analyses were performed in the intention-to-treat population. NA denotes not applicable.
† The primary safety outcome was a composite of major cardiovascular events (cardiovascular death, myocardial infarction, or stroke) ($P<0.001$ for noninferiority at the interim analysis; $P<0.001$ for noninferiority and 0.85 for superiority at trial completion).
‡ The primary cardiovascular efficacy outcome (extended major cardiovascular events) was a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or any coronary revascularization ($P=0.55$ for superiority).
§ All the patients in this category (2015 in the lorcaserin group and 1976 in the placebo group) had prediabetes at baseline.

events (Table 3). Adverse events that were deemed by investigators to be possibly related to a trial agent and leading to discontinuation of lorcaserin or placebo were more frequent in the lorcaserin group than in the placebo group (in 433 of 5995 patients [7.2%] vs. 220 of 5992 [3.7%]). The most commonly reported adverse events leading to discontinuation in the lorcaserin group were dizziness, fatigue, headache, diarrhea, and nausea (Table 3). The occurrence of prespecified adverse events of special interest was low (<1% for most events). Suicidal ideation or behavior was reported in 21 patients (0.4%) in the lorcaserin group and 11 patients (0.2%) in the placebo group ($P=0.08$); the numerical imbalance in suicidal ideation or behavior appeared to be restricted to patients with depression at baseline (in 15 patients [1.2%] and 6 patients [0.5%], respectively; $P=0.06$). There were no deaths by suicide. Hypoglycemia occurred in 232 patients (3.9%) in the lorcaserin group and 202 (3.4%) in the placebo group ($P=0.14$) (Table 3). Severe hypoglycemia with serious complications (i.e., that required hospitalization, were life-threatening or disabling, or resulted in death) was rare but more common with lorcaserin than with placebo (in 13 patients [0.2%] vs. 4 patients [0.1%]), with the imbalance restricted to hypoglycemia requiring hospitalization (11 patients vs. 2 patients). All but 1 event occurred in patients with diabetes who were receiving insulin or a sulfonylurea at baseline (12 vs. 4 events, $P=0.054$).

ECHOCARDIOGRAPHIC SUBSTUDY

Among the 3270 patients for whom echocardiographic data were available at baseline and at 1 year, new or worsening FDA-defined valvulopathy had occurred in 30 of 1624 patients (1.8%) in the lorcaserin group and in 22 of 1646 (1.3%) in the placebo group ($P=0.24$) (Table 3). The nonsignificant numerical imbalance between the groups was due to more patients in the lorcaserin group than in the placebo group with new-onset, mild aortic-valve insufficiency (23 patients vs. 15 patients). None of the patients with valvulopathy were symptomatic, were hospitalized, or required valve replacement or repair. Findings were similar in a

sensitivity analysis with the use of multiple imputation that included all 4318 patients in the echocardiographic substudy (see the Supplementary Appendix).

In the total population of 12,000 patients, symptomatic valvular heart disease of any type was diagnosed in 58 patients in the lorcaserin group and in 64 in the placebo group. Of these patients, 20 in the lorcaserin group and 23 in the placebo group met the specific FDA-defined criteria for valvulopathy.

The change in pulmonary artery systolic pressure at 1 year was similar in the two groups (least-squares mean change, −1.0 mm Hg [95% CI, −1.4 to −0.5] with lorcaserin and −0.7 mm Hg [95% CI, −1.1 to −0.3] with placebo; P=0.32). At 1 year, new or worsening pulmonary hypertension occurred in 13 of 813 patients (1.6%) in the lorcaserin group and in 8 of 825 (1.0%) in the placebo group (P=0.26). Two patients in each group had symptoms leading to mild limitation in activity; the remainder of patients were asymptomatic. Pulmonary vasodilator therapy for pulmonary hypertension was not initiated in any of the patients, and none of the patients were hospitalized.

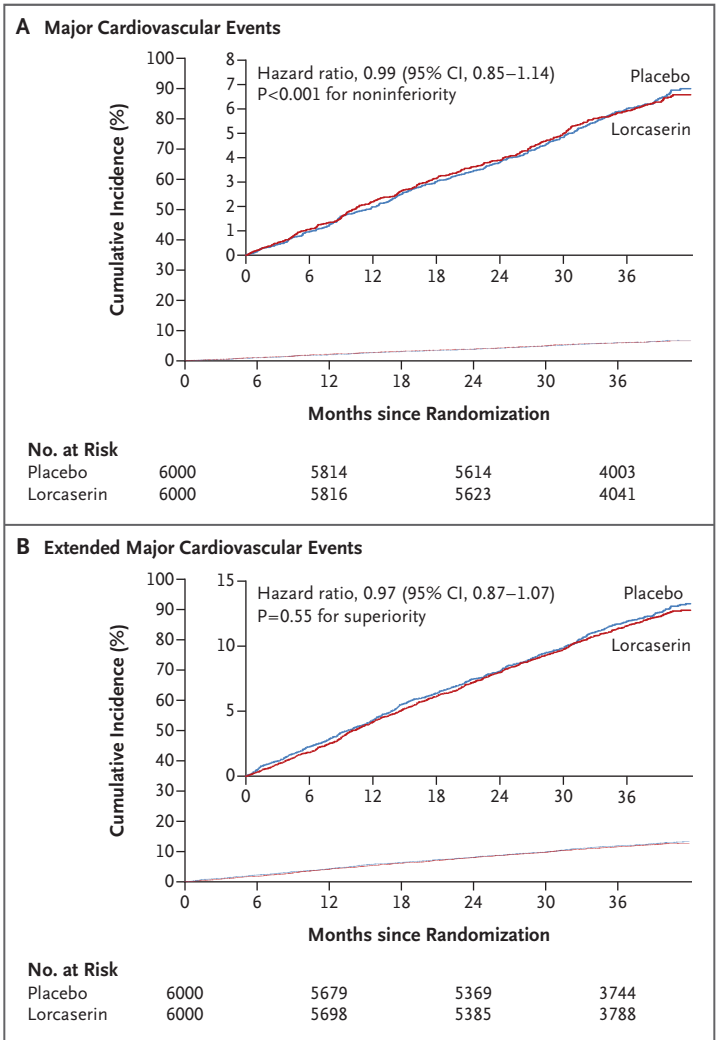

Figure 2. Major Adverse Cardiovascular Outcomes.

Shown are the cumulative incidences of the primary safety outcome of major cardiovascular events (a composite of cardiovascular death, myocardial infarction, or stroke) (Panel A) and the primary cardiovascular efficacy outcome of major cardiovascular events plus hospitalization for unstable angina, heart failure, or coronary revascularization (extended major cardiovascular events) (Panel B) among patients in the lorcaserin group and the placebo group. The insets show the data on an expanded y axis. The hazard ratios are for noninferiority of lorcaserin regarding major cardiovascular events and for superiority of lorcaserin regarding extended major cardiovascular events.

DISCUSSION

Lorcaserin was previously shown to be efficacious for weight loss, which led to approval by the FDA for long-term weight management in obese or overweight patients who had at least one weight-related coexisting condition.[12-14] In addition to observing persistent weight loss with an extended duration of use of lorcaserin, we found that the drug also met the FDA-mandated criteria for cardiovascular safety.

In previous studies, patients who received lorcaserin had 3 to 4% greater weight loss than those who received placebo, with a larger proportion of patients in the lorcaserin group with weight loss of at least 5% or at least 10% at 1 year.[12-14] In our trial, treatment with lorcaserin along with lifestyle interventions resulted in a net mean weight loss of 2.7% at 1 year and more than tripled the odds of having a weight loss of at least 5% or at least 10%, as compared with placebo. The difference remained significant through 40 months of follow-up. To put these findings in perspective, lifestyle interventions typically result in a weight loss of 2 to 10%; the rate is 2 to 10% with pharmacotherapy and a more durable 15 to 60% with bariatric surgery.[5,6,16,17]

Associated with the described weight loss, we observed reductions in triglyceride levels and in dysglycemia, a finding that was consistent with an overall picture of an improved metabolic pro-

Table 3. Adverse Events.*

Adverse Events	Lorcaserin (N=5995)	Placebo (N=5992)	Absolute Risk Difference (95% CI)†
			percentage points
Any adverse event — no. (%)			
Serious adverse event	1882 (31.39)	1931 (32.23)	–0.84 (–2.50 to 0.83)
Adverse event possibly caused by trial agent and leading to discontinuation‡	433 (7.22)	220 (3.67)	3.55 (2.75 to 4.37)
Dizziness	80 (1.33)	16 (0.27)	1.06 (0.76 to 1.32)
Fatigue	67 (1.12)	6 (0.10)	1.02 (0.76 to 1.32)
Headache	37 (0.62)	15 (0.25)	0.37 (0.14 to 0.62)
Nausea	36 (0.60)	19 (0.32)	0.28 (0.04 to 0.54)
Diarrhea	27 (0.45)	17 (0.28)	0.17 (–0.05 to 0.40)
Adverse event of special interest — no. (%)			
Any cancer	215 (3.59)	210 (3.50)	0.09 (–0.58 to 0.75)
Ductal carcinoma in situ	3 (0.05)	2 (0.03)	0.02 (–0.08 to 0.12)
Fibroadenoma	4 (0.07)	1 (0.02)	0.05 (–0.03 to 0.16)
Euphoria	5 (0.08)	1 (0.02)	0.06 (–0.02 to 0.18)
Psychosis	16 (0.27)	12 (0.20)	0.07 (–0.11 to 0.25)
Suicidal ideation or behavior	21 (0.35)	11 (0.18)	0.17 (–0.02 to 0.37)
Death by suicide	0	0	NA
Serotonin syndrome	3 (0.05)	3 (0.05)	0.00 (–0.10 to 0.10)
Priapism	1 (0.02)	3 (0.05)	–0.03 (–0.13 to 0.05)
Other adverse event — no. (%)			
Any hypoglycemia§	232 (3.87)	202 (3.37)	0.50 (–0.17 to 1.17)
Mild	97 (1.62)	90 (1.50)	0.12 (–0.33 to 0.57)
Moderate	100 (1.67)	93 (1.55)	0.12 (–0.34 to 0.57)
Severe	22 (0.37)	15 (0.25)	0.12 (–0.09 to 0.33)
Severe with serious complications¶	13 (0.22)	4 (0.07)	0.15 (0.02 to 0.31)
Requiring hospitalization	11 (0.18)	2 (0.03)	
Life-threatening or disabling	2 (0.03)	2 (0.03)	
Leading to death	0	0	
Echocardiographic substudy — no./total no. (%)‖			
New or worsening FDA-defined valvulopathy at 1 yr	30/1624 (1.85)	22/1646 (1.34)	0.51 (–0.36 to 1.42)
New or worsening pulmonary hypertension at 1 yr	13/813 (1.60)	8/825 (0.97)	0.63 (–0.50 to 1.86)

* Events were measured in the safety population while the patients were receiving the trial agents. The 95% confidence intervals were calculated with the use of the Miettinen–Nurminen method. FDA denotes Food and Drug Administration, and NA not applicable.

† The difference is for the percentage in the lorcaserin group minus the percentage in the placebo group.

‡ Listed are adverse events that were most common in the lorcaserin group and that were determined by the investigators to be possibly caused by lorcaserin, which led to the discontinuation of the trial agent.

§ Hypoglycemia was reported as the most severe event and most serious complication on a per-patient basis in the total safety population (i.e., patients with and those without a baseline history of diabetes).

¶ Other categories for the severity of hypoglycemia are provided in the Supplementary Appendix.

‖ Listed are events in patients for whom data were available at baseline and at 1 year.

file. In addition, there were slightly lower values for heart rate and blood pressure than with placebo. In contrast, most other weight-loss agents cause an increase in heart rate and, in some instances, blood pressure.[18-20] The appetite suppressant sibutramine, a norepinephrine and serotonin-reuptake inhibitor, was associated with measures of heart rate and blood pressure, as well as with rates of stroke and myocardial infarction, that were higher than those with placebo, findings that resulted in the removal of the drug from the market.[9]

The experience with other weight-loss drugs has also been challenging owing to unacceptable safety profiles. Peripheral activation of the 2B serotonin receptor subtypes (5HT-2BR) on cardiovascular tissues by fenfluramine and its derivatives resulted in the relatively rapid development of pulmonary hypertension and valvular heart disease.[21] Blockade of the endocannabinoid receptor with rimonabant was safe from a cardiovascular perspective but resulted in unacceptably high rates of serious, neuropsychiatric side effects.[10] Counterbalancing these serious safety concerns is the scope of the obesity epidemic. Thus, the FDA has allowed approval of weight-loss agents contingent on the ability to rule out an increased risk of adverse cardiovascular outcomes in a dedicated postmarketing safety trial.[22]

In our trial, lorcaserin was not associated with any increase in cardiovascular risk among patients at high cardiovascular risk. However, there was no significant between-group difference in major adverse cardiovascular outcomes in the overall population. Indeed, no other specific lifestyle or pharmacologic weight-loss strategy has yet to result in a reduction in cardiovascular events. The antidiabetic medication liraglutide, a GLP-1 receptor agonist, was associated with a reduction in the rate of major cardiovascular events, including death, in patients with type 2 diabetes who received the daily dose of 1.8 mg that was approved for glucose lowering. However, the cardiovascular safety and efficacy of the higher weight-loss dose (3.0 mg daily) has not been assessed to date.[23] Observational studies of bariatric surgery, which has resulted in a much better rate of sustained weight loss than pharmacologic or lifestyle-modification strategies, have also shown an association with lower rates of death, myocardial infarction, stroke, and heart failure during 10 to 20 years of follow-up. However, no randomized trials of bariatric strategies that have been completed to date have had the statistical power to assess major adverse cardiovascular events.[21,24-26]

It is possible that weight loss alone does not have an effect on the risk of major adverse cardiovascular events or that the more modest weight reductions that are typically observed with pharmacologic or lifestyle strategies must be sustained for an extended period to lower cardiovascular risk. However, in the Look AHEAD (Action for Health in Diabetes) trial, intensive lifestyle interventions, as compared with the standard of care, did not alter the risk of cardiovascular events among obese patients with diabetes over a 10-year follow-up period.[27]

In our trial, the most commonly reported adverse events that were ascribed to lorcaserin and that led to treatment discontinuation were dizziness, fatigue, headache, diarrhea, and nausea, all of which have been reported in previous trials.[12-14] Hypoglycemia has been previously observed to be more frequent in patients with diabetes receiving lorcaserin than in those receiving placebo. In our trial, severe hypoglycemia with serious complications was significantly more common in the lorcaserin group than in the placebo group, with all but one event occurring in patients with diabetes who were receiving insulin or a sulfonylurea.[14]

Lorcaserin has minimal cross-reactivity with other serotonin-receptor subtypes and does not alter the release or metabolism of serotonin; thus, it is not considered to pose a clinically important risk of adverse events such as the serotonin syndrome, pulmonary hypertension, or valvulopathy.[28,29] Patients in the lorcaserin group had a numerical, but not significant, imbalance in FDA-defined valvulopathy and pulmonary hypertension. Since the overall event rates were low, we cannot rule out a rate of new or worsening valvulopathy that was 0.4% lower or 1.4% higher with lorcaserin than with placebo at 1 year, along with a rate of new or worsening pulmonary hypertension that was 0.5% lower or 1.9% higher. However, all events of new or worsening valvulopathy that were identified in the echocardiographic substudy at 1 year were subclinical. In contrast, patients who had toxic effects associated with fenfluramine–phentermine presented with symptomatic valvular heart disease at an average of 1 year after

the initiation of therapy.[8] Moreover, in the full cohort of 12,000 patients who were followed for a median of 3.3 years in our trial, there was no imbalance in symptomatic cases of FDA-defined valvulopathy. In terms of incident pulmonary hypertension, all but 4 patients (2 in each group) were asymptomatic. We are not able to comment on the safety profile beyond the period studied.

In conclusion, among overweight or obese patients with atherosclerotic cardiovascular disease or multiple cardiovascular risk factors who were being treated with dietary and exercise interventions, those who received lorcaserin had better long-term rates of weight loss than those who received placebo at a median follow-up of 3.3 years. The higher weight-loss rates were achieved without an accompanying increase in the risk of cardiovascular events.

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APPENDIX

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REFERENCES

1. Obesity and overweight fact sheet. Geneva: World Health Organization, 2016 (http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight).
2. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. JAMA 2018;319:1723-5.
3. The GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 2017;377:13-27.
4. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 2013;309:71-82.
5. Bray GA, Heisel WE, Afshin A, et al. The science of obesity management: an Endocrine Society scientific statement. Endocr Rev 2018;39:79-132.
6. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society. Circulation 2014; 129:Suppl 2:S102-S138.
7. Garvey WT, Garber AJ, Mechanick JI, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. Endocr Pract 2014;20:977-89.
8. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine–phentermine. N Engl J Med 1997;337:581-8.
9. James WPT, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 2010;363: 905-17.
10. Topol EJ, Bousser MG, Fox KA, et al. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. Lancet 2010;376:517-23.
11. Brashier DB, Sharma AK, Dahiya N, Singh SK, Khadka A. Lorcaserin: a novel antiobesity drug. J Pharmacol Pharmacother 2014;5:175-8.
12. Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med 2010;363:245-56.
13. Fidler MC, Sanchez M, Raether B, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. J Clin Endocrinol Metab 2011;96:3067-77.
14. O'Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring) 2012;20: 1426-36.
15. Bohula EA, Scirica BM, Fanola C, et al. Design and rationale for the Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients-Thrombolysis in Myocardial Infarction 61 (CAMELLIA-TIMI 61) trial. Am Heart J 2018;202:39-48.
16. Leblanc ES, O'Connor E, Whitlock EP, Patnode CD, Kapka T. Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2011;155:434-47.
17. Hiatt WR, Thomas A, Goldfine AB. What cost weight loss? Circulation 2012; 125:1171-7.

18. Nissen SE, Wolski KE, Prcela L, et al. Effect of naltrexone-bupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors: a randomized clinical trial. JAMA 2016;315:990-1004.
19. Vorsanger MH, Subramanyam P, Weintraub HS, et al. Cardiovascular effects of the new weight loss agents. J Am Coll Cardiol 2016;68:849-59.
20. Jordan J, Astrup A, Engeli S, Narkiewicz K, Day WW, Finer N. Cardiovascular effects of phentermine and topiramate: a new drug combination for the treatment of obesity. J Hypertens 2014; 32:1178-88.
21. Sjöström L, Narbro K, Sjöström CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007;357:741-52.
22. Guidance for industry: developing products for weight management. Rockville, MD: Food and Drug Administration, 2007 (https://www.fda.gov/downloads/Drugs/Guidances/ucm071612.pdf).
23. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311-22.
24. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. JAMA 2012;307: 56-65.
25. Sundström J, Bruze G, Ottosson J, Marcus C, Näslund I, Neovius M. Weight loss and heart failure: a nationwide study of gastric bypass surgery versus intensive lifestyle treatment. Circulation 2017;135: 1577-85.
26. Zhou X, Yu J, Li L, et al. Effects of bariatric surgery on mortality, cardiovascular events, and cancer outcomes in obese patients: systematic review and meta-analysis. Obes Surg 2016;26:2590-601.
27. The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145-54.
28. Meltzer HY, Roth BL. Lorcaserin and pimavanserin: emerging selectivity of serotonin receptor subtype-targeted drugs. J Clin Invest 2013;123:4986-91.
29. Thomsen WJ, Grottick AJ, Menzaghi F, et al. Lorcaserin, a novel selective human 5-hydroxytryptamine2C agonist: in vitro and in vivo pharmacological characterization. J Pharmacol Exp Ther 2008; 325:577-87.