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Cardiovascular And Metabolic
Effects of Lorcaserin In Overweight And Obese Patients
TIMI 61

Cardiovascular safety & efficacy of lorcaserin in overweight and obese patients

Primary results from the CAMELLIA-TIMI 61 Trial

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on behalf of the CAMELLIA-TIMI 61 Investigators

An Academic Research Organization of
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Weight Loss Agents

- Weight loss can improve CV risk factors, but is difficult to achieve and maintain
- Weight loss agents are guideline-recommended adjuncts to lifestyle modification[1, 2]
- However, no agent has convincingly demonstrated CV safety in a rigorous clinical outcomes study
- In fact, several agents have been shown to precipitate CV or psychiatric side effects
- US FDA mandate to demonstrate CV safety for all weight loss agents

[1]2013 AHA/ACC/TOS Guideline, Circulation 2014;129:S102
[2]2014 AACE/ACE Position Statement, Endocr Pract 2014;20:977

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Lorcaserin

- Selective agonist of serotonin (5HT)-2C receptor
- Hypothalamic activation of the POMC (pro-opiomelanocortin) pathway → appetite suppression
- Based on phase 3 studies testing weight loss efficacy, approved for use in the US for chronic weight management

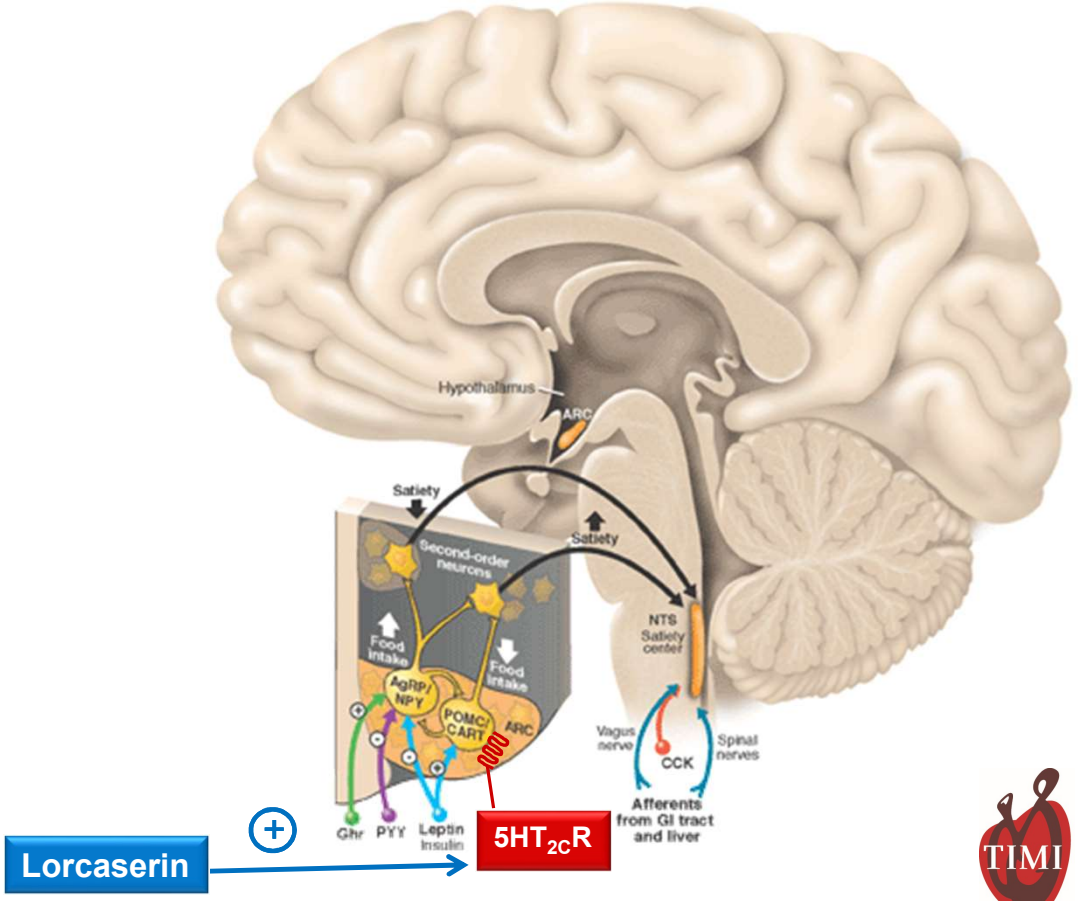

Image modified from Marx J. *Science*. 2003;299:846-849.

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Trial Organization

Executive Committee

Marc S. Sabatine (Chair)	Benjamin M. Scirica (Co-PI)	Darren K. McGuire	Anthony Keech
Stephen D. Wiviott (Co-PI)	Silvio Inzucchi	Steven R. Smith	

TIMI Study Group

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Sponsor: Eisai

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Independent Data Monitoring Committee

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Sheryl Kelsey (Stats)			

Steering Committee & National Lead Investigators (NLI)

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Trial Schema

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Obese or Overweight (BMI≥27kg/m²)
Established CV disease* or
T2DM & other CV risk factors†

N = 12,000

Exercise & Reduced-Calorie Diet

Lorcaserin 10mg BID

RANDOMIZE 1:1 DOUBLE BLIND
Stratified by CV disease or CV RF

PLACEBO

Follow up visits Q 3mo x 2yr then Q 4mo

Interim Analysis *(Safety)*

End of Treatment *(Efficacy)*

Median Follow up: 3.3 yrs

Primary Safety: Non-inferiority for MACE with boundary of 1.4

Efficacy: Superiority for MACE+

Primary CV Safety EP: MACE (CV Death, MI, CVA)
Primary CV Efficacy EP: MACE+ (MACE, Hosp for HF or UA, cor revasc)

**Coronary, cerebrovascular or peripheral artery disease; †T2DM with ≥1 of following: HTN, HL, hsCRP>3, eGFR 30-60, albuminuria*

Bohula EA et al. *Am Heart J* 2018;202:39-48

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Other Outcomes

- **Other Efficacy**
  - Incident diabetes
- **Safety**
  - Events of interest incl. malignancy, psychiatric events, serotonin syndrome, hypoglycemia, valvulopathy and pulmonary HTN
  - Dedicated echo sub-study in 4318 pts, ~20,000 serial echos
- **TIMI Clinical Events Committee (CEC)**
  - Adjudicated all CV endpoints & new-onset diabetes
  - Members unaware of treatment assignment

Bohula EA et al. *Am Heart J* 2018;202:39-48

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Baseline Characteristics

Characteristic (N=12,000)	Value
Age (median, IQR)	64 [58, 69]
Male, %	64
Weight in kg (median, IQR)	102 [90, 116]
BMI in kg/m^2 (median, IQR)	35 [32, 39]
Multiple CV Risk Factor, %	25
Established CV Disease, %	75
Coronary artery disease	68
Peripheral arterial disease	5.5
Cerebrovascular disease	9.4
Hypertension, %	90
Hyperlipidemia, %	94
eGFR < 60 ml/min/1.73m^2, %	20
Pre-diabetes, %	33
Diabetes, %	57

Pooled data; no differences between treatment arms

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Trial Metrics

Median Follow-up: 3.3 yrs

	Lorcaserin N=6,000	Placebo N=6,000
Study Drug Discontinuation, %/yr	12.0	12.7
Lost-to-follow-up, %/yr	0.2	0.3
Withdrawal of Consent, %/yr	0.6	0.7
Completed Study*, %	98	97

**Had visit during study closure or died during follow up*

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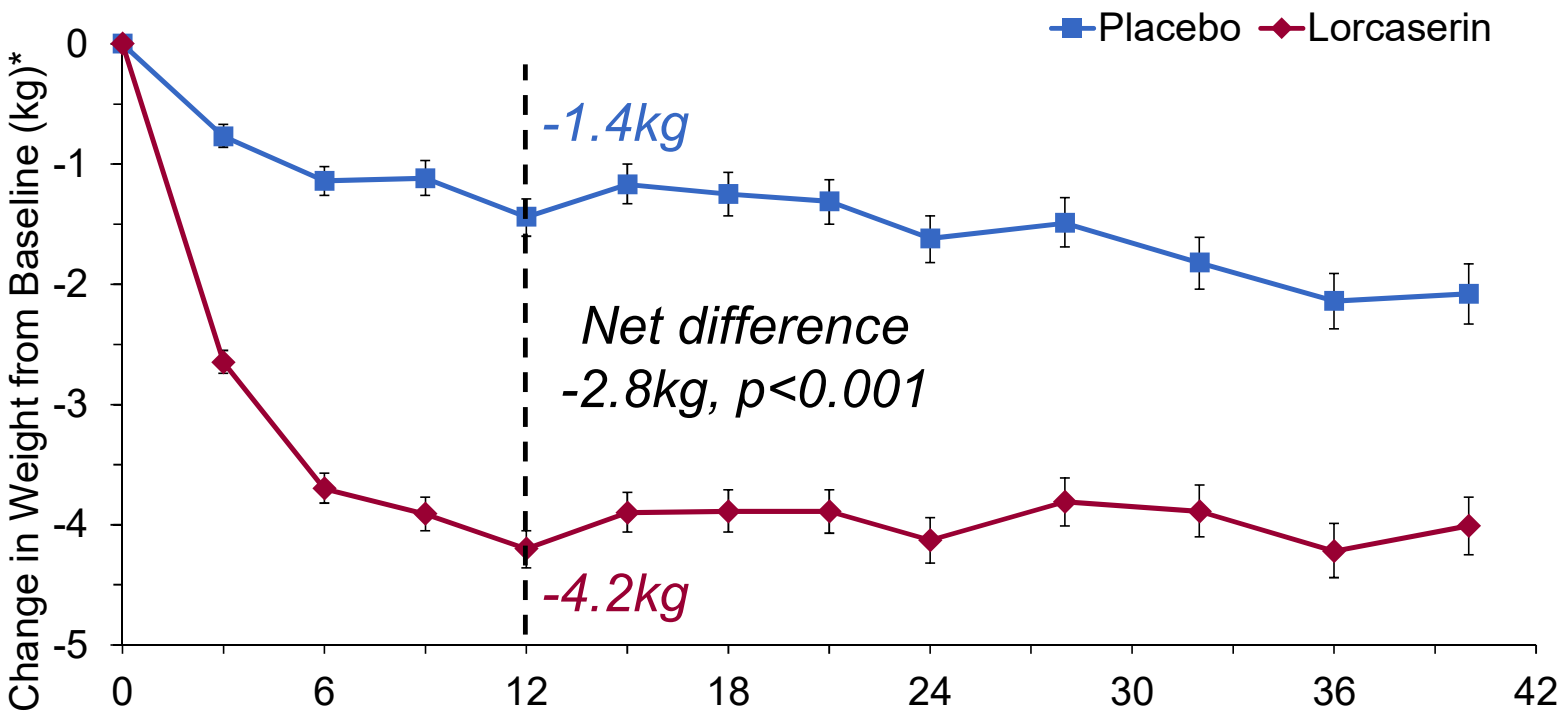
Weight Loss

On a background of lifestyle interventions:



**Least-squared means*

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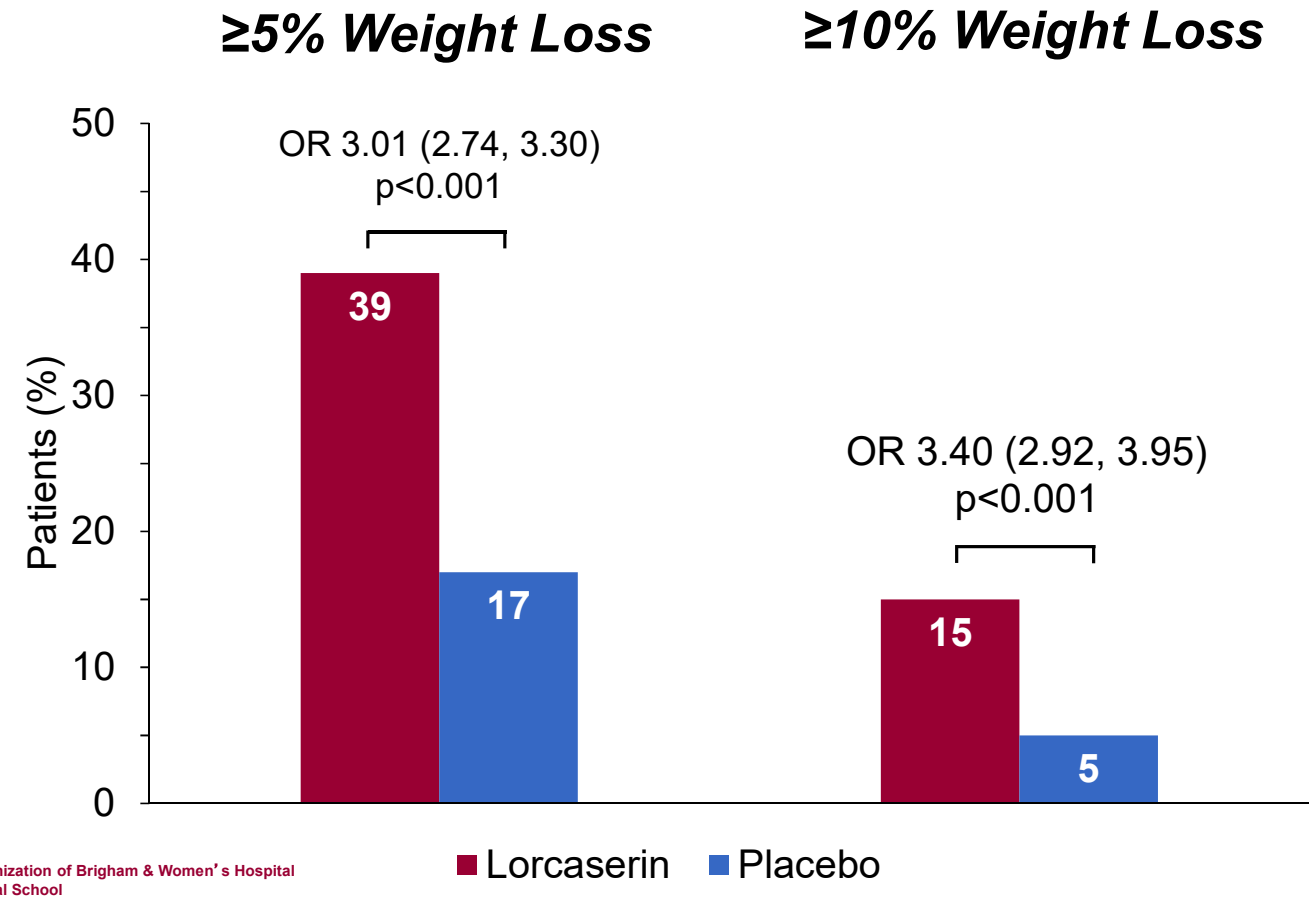
Weight Loss at 1 Year



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Cardiovascular Risk Factors

		Treatment Difference at 1 Year		
	Baseline Median (IQR)	**Value**	**95% CI**	**P-value**
SBP (mm Hg)	130 (120-140)	-0.9	(-1.4, -0.4)	0.001
HR (bpm)	67 (60-74)	-1.0	(-1.3, -0.7)	<0.001
Triglycerides (mg/dL)	133 (98-184)	-11.7	(-14.7, -8.7)	<0.001
HbA1c (%)	6.1 (5.6-7.0)	-0.2	(-0.3, -0.2)	<0.001

Least-squared means difference (Placebo – Lorcaserin) at 1 Year

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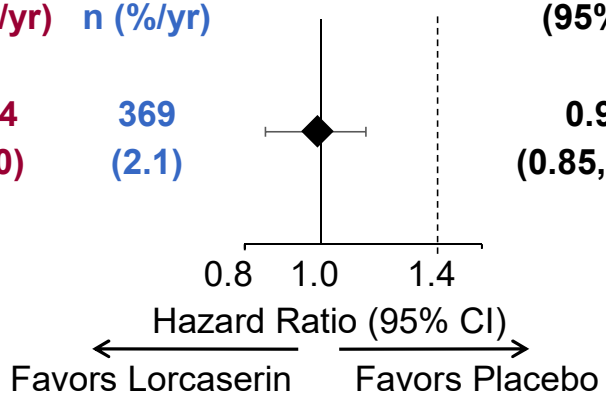
Primary CV Outcomes

N = 12,000

CV Death, MI, Stroke (Safety)

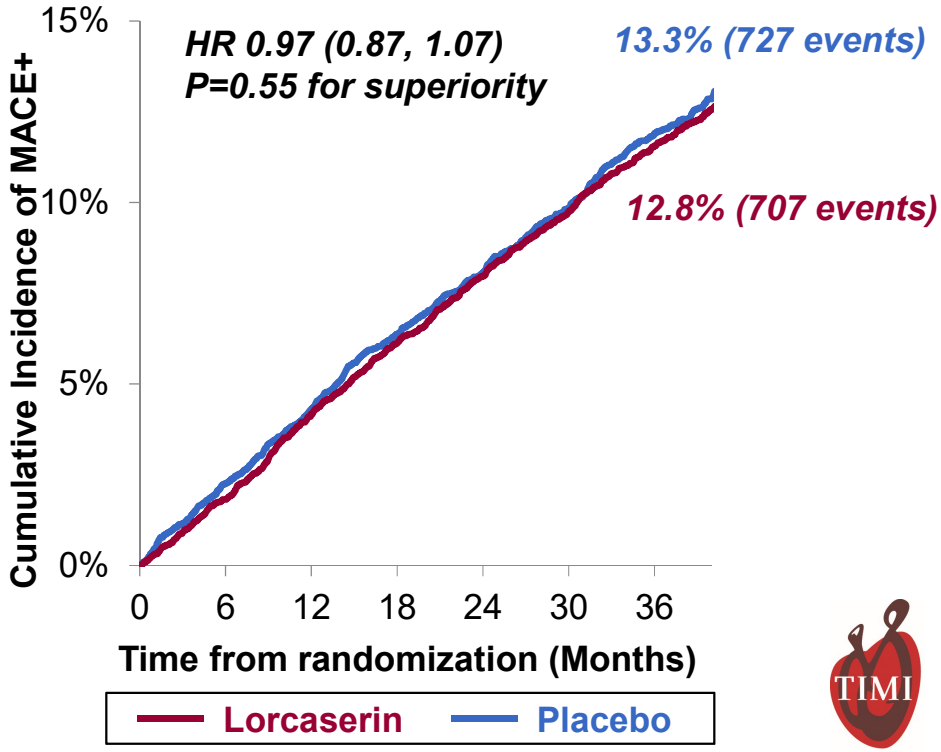
	Lorc n (%/yr)	Pbo n (%/yr)	MACE HR (95%CI)
CV death, MI, or stroke	364 (2.0)	369 (2.1)	0.99* (0.85, 1.14)



P (non-inferiority) < 0.001

***Non-inferiority boundary: HR 97.5% upper bound of 1.4**

CV Death, MI, Stroke, HF, Hosp for UA, Cor Revasc (Efficacy)



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Individual Outcomes

	Lorcaserin N=6,000 %/yr	Placebo N=6,000 %/yr	HR (95% CI)
MACE	2.0	2.1	0.99 (0.85, 1.14)*
MACE+	4.1	4.2	0.97 (0.87, 1.07)
CV death	0.49	0.47	1.04 (0.78, 1.40)
MI	1.2	1.3	0.99 (0.82, 1.19)
Stroke	0.46	0.54	0.86 (0.64, 1.15)
Heart failure	0.78	0.83	0.95 (0.76, 1.20)
Unstable angina	0.50	0.43	1.16 (0.86, 1.57)
Coronary Revasc	2.3	2.3	0.98 (0.86, 1.12)
Incident diabetes†	3.1	3.8	0.81 (0.66, 0.99)

**Non-inferiority boundary for 1-sided 97.5% upper bound of 1.4;*
†In patients with pre-diabetes at baseline

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Adverse Events

	Lorcaserin N=5,995 %	Placebo N=5,992 %
Serious Adverse Events†	31	32
AE possibly due to study drug → drug discontinuation	7.2	3.7
Dizziness	1.3	0.3
Fatigue	1.1	0.1
Headache	0.6	0.3
Nausea	0.6	0.3

†p-value = NS; % refers to n/N

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Adverse Events

	Lorcaserin N=5,995 %	Placebo N=5,992 %
Investigator-Reported Adverse Events		
Malignant neoplasms	3.6	3.5
Euphoria	0.08	0.02
Psychosis	0.3	0.2
Suicidal ideation or behavior	0.4	0.2
Death by suicide	0	0
Serotonin syndrome	0.05	0.05
Any hypoglycemia	3.9	3.4
Severe w/ complications†	0.2	0.1
Echocardiographic Sub-Study	N=2,151	N=2,167
FDA-defined valvulopathy at 1 yr*‡	1.8	1.3
Pulmonary hypertension at 1 yr‡	1.6	1.0

†p-value<0.05

**≥mild aortic regurgitation or ≥moderate mitral regurgitation*

‡ In patients with non-missing baseline and 1 year data in echocardiographic substudy

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Summary

On a background of lifestyle interventions in overweight or obese patients at high CV risk, lorcaserin:

- ***Resulted in sustained weight loss and modest improvements in CV risk factors***
- ***Did not increase the risk of MACE***
- ***Favorable effects on glycemia (full metabolic data at EASD in Berlin, Oct 4th 2018)***

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Conclusion

Lorcaserin is the first pharmacologic weight loss agent with proven safety for major adverse CV events supporting its role as an adjunct to lifestyle modification for long-term weight management even in patients at high CV risk.

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ORIGINAL ARTICLE

Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients

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