Camellia
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

BWH
An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School
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Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Personal consulting fees from Merck, Novartis, Servier, Daiichi Sankyo, Medscape, MD Conference Express, Lexicon)
- Research contracts (Eisai is the trial sponsor and provides research grants to my institution)

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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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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

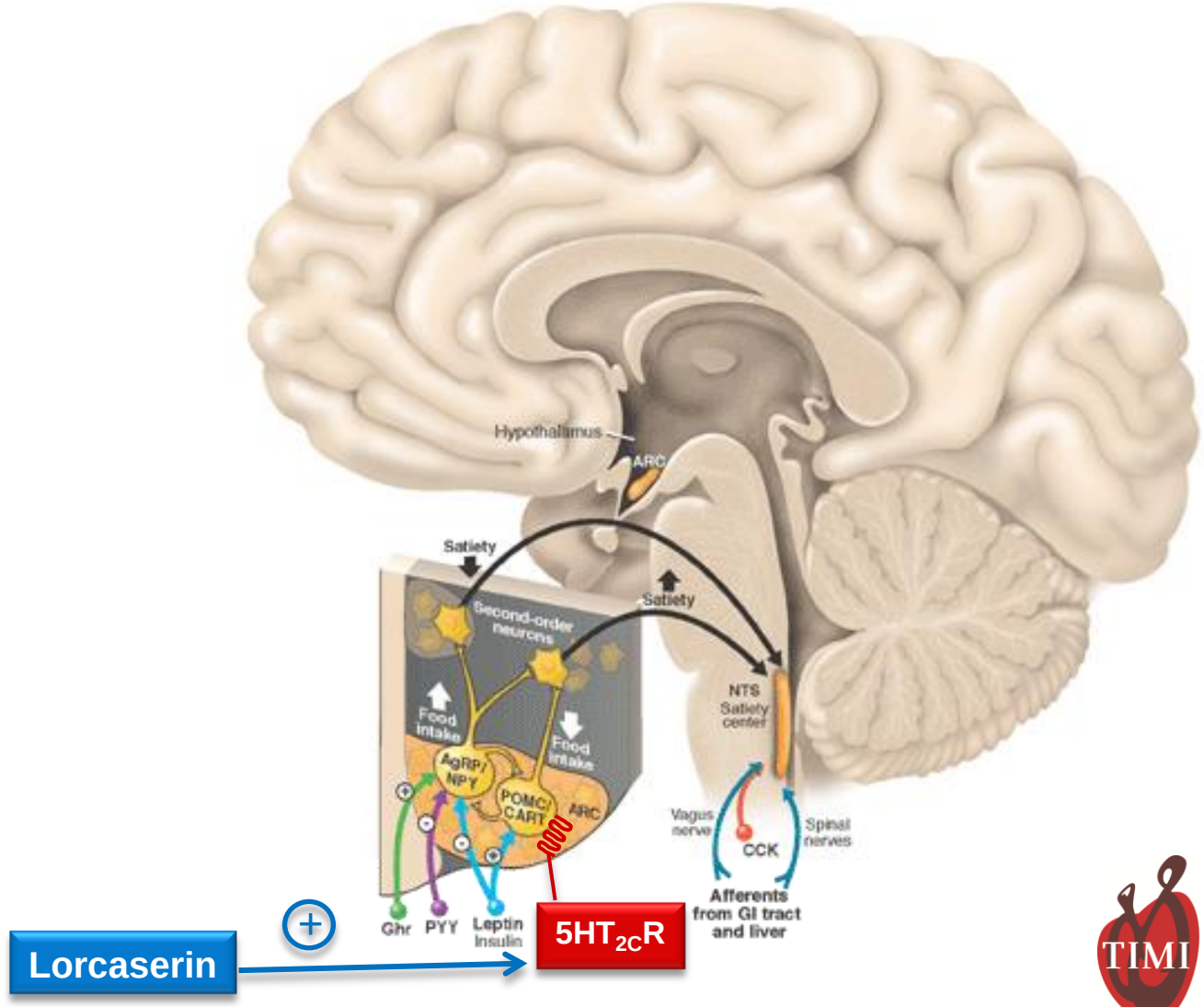

Image modified from Marx J. *Science.* 2003;299:846-849.

Trial Schema

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TIMI

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*

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

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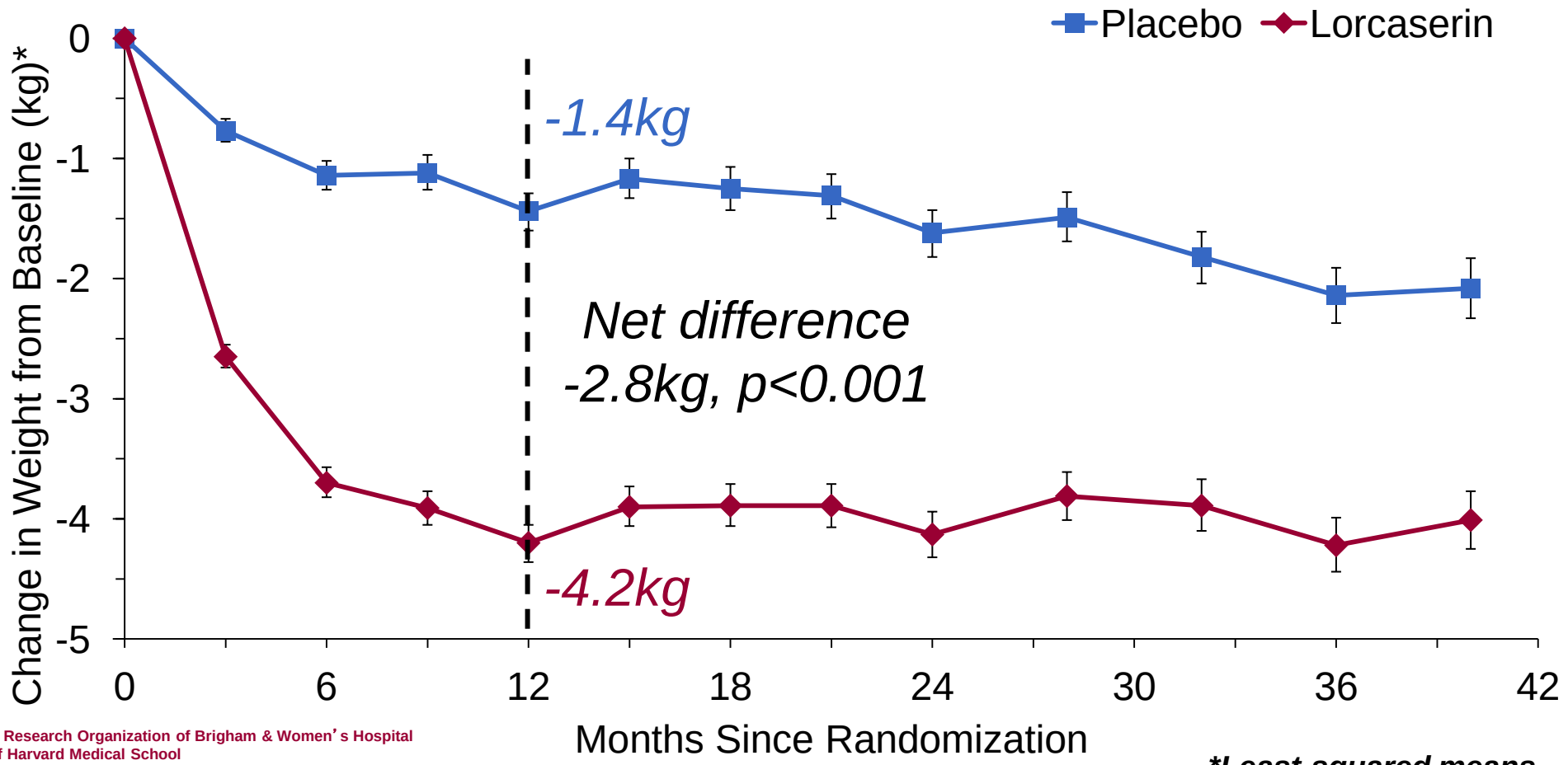
Weight Loss

On a background of lifestyle interventions:



**Least-squared means*

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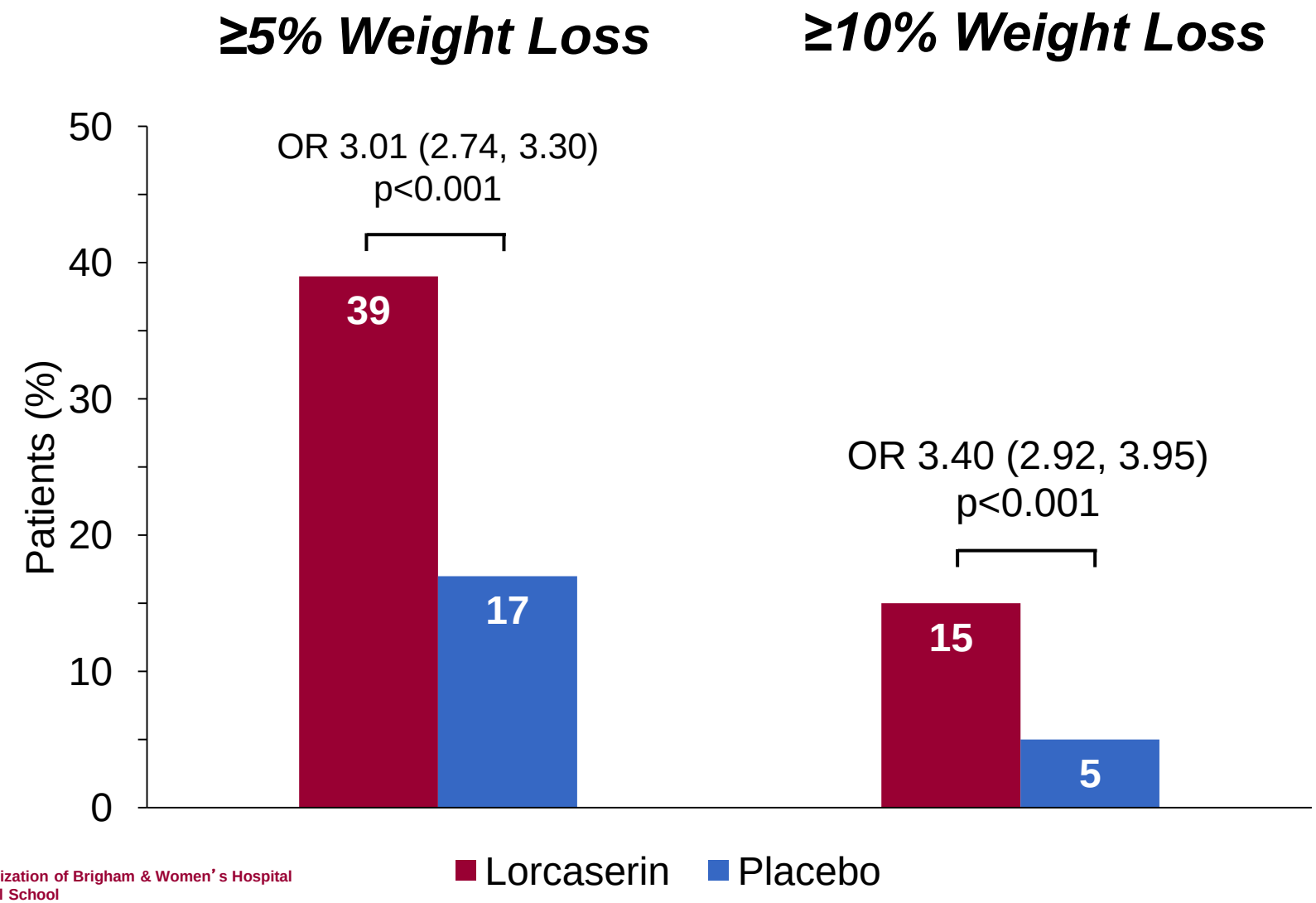
Weight Loss at 1 Year



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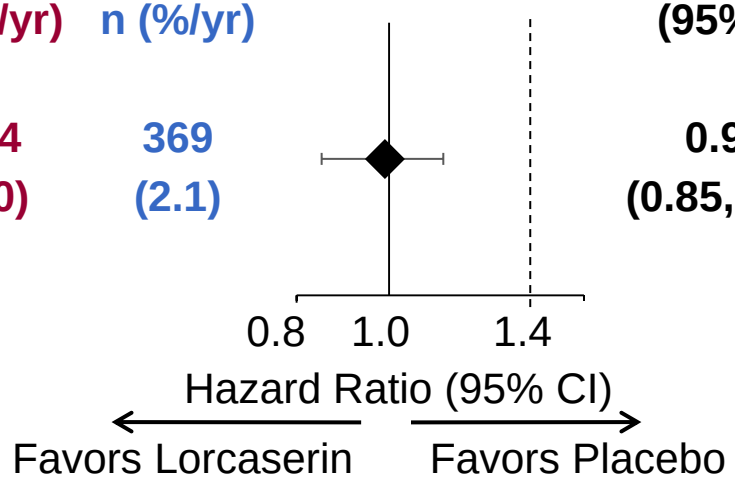
Primary CV Outcomes

N = 12,000

CV Death, MI, Stroke (Safety)

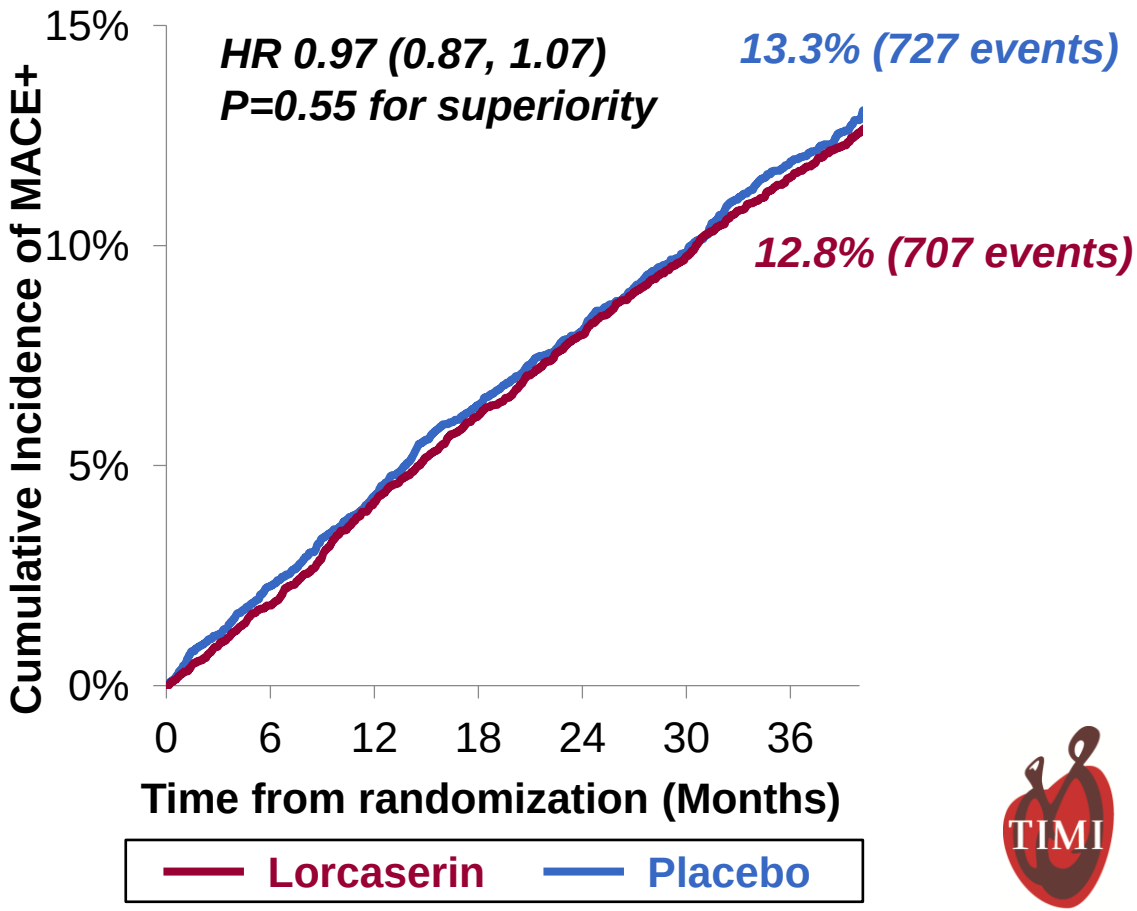
	Lorc n (%/yr)	Pbo n (%/yr)	MACE HR (95%CI)
CV death, MI, or stroke	364 (2.0)	369 (2.1)	0.99* (0.85, 1.14)



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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Adverse Events

	Lorcaserin N=5,995 %	Placebo N=5,992 %
Investigator-Reported Clinical 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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Key Message

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.