

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*

Declaration of interest

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

¹2013 AHA/ACC/TOS Guideline, *Circulation* 2014;129:S102

²2014 AACE/ACE Position Statement, *Endocr Pract* 2014;20:977

- 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

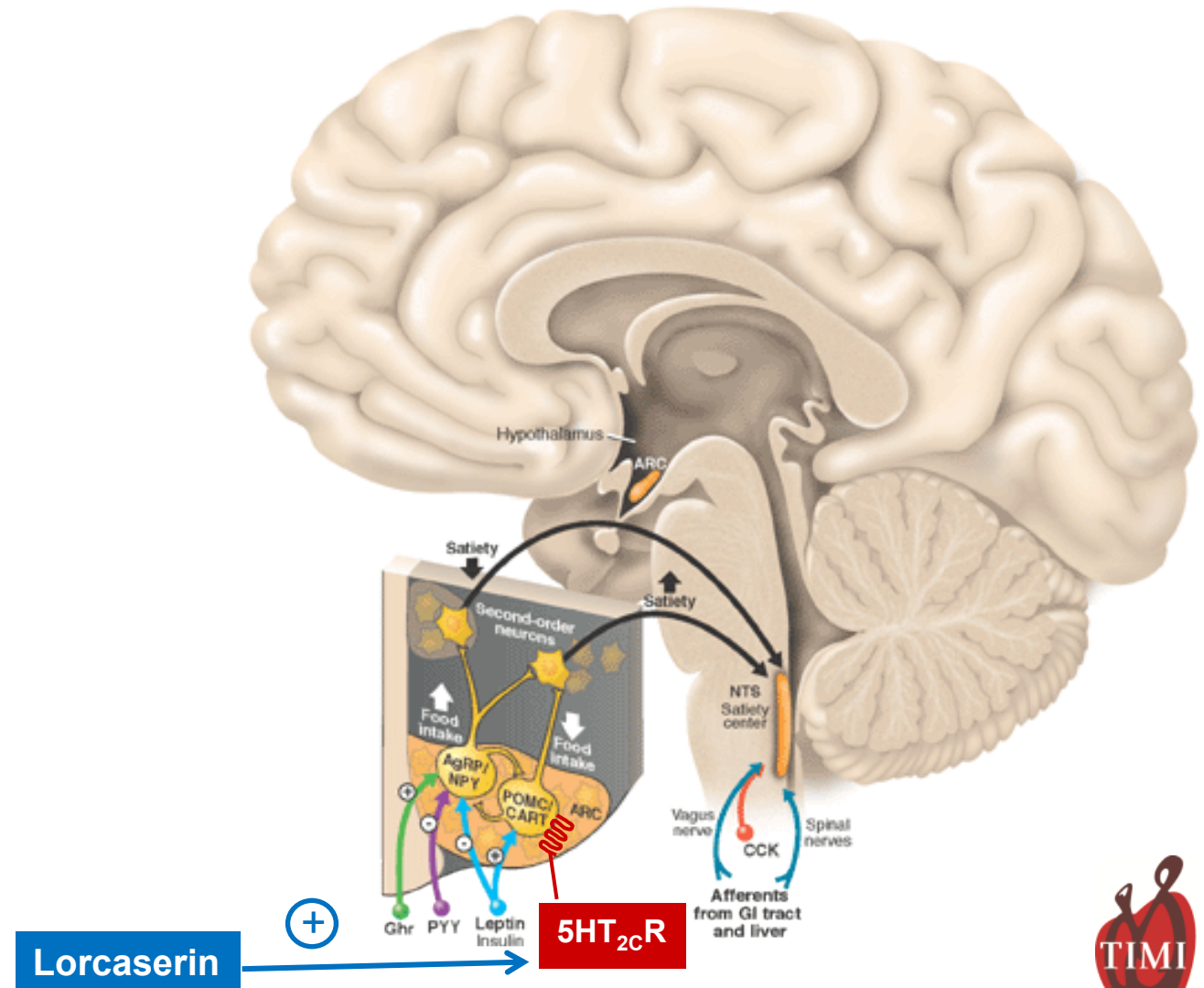


Image modified from Marx J. *Science*. 2003;299:846-849.

Trial Organization

Executive Committee

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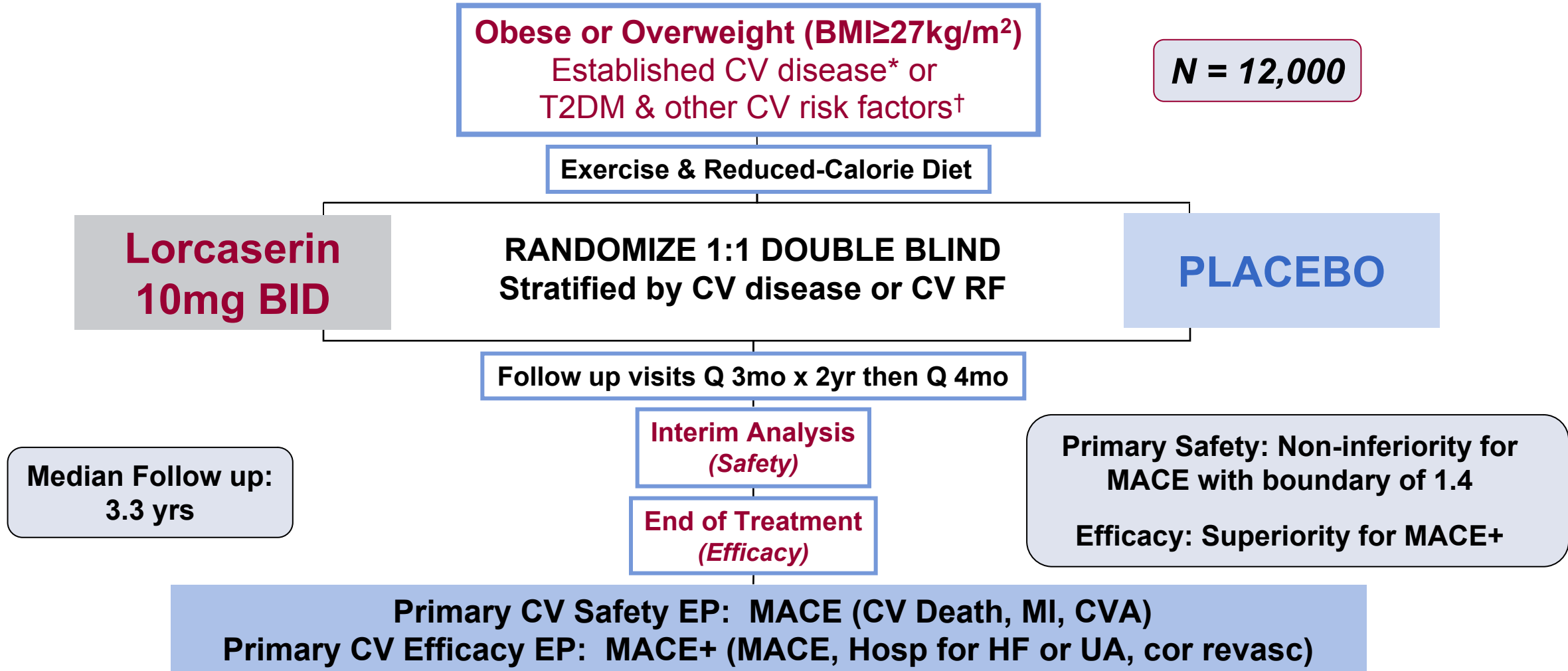
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Trial Schema



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

- **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

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

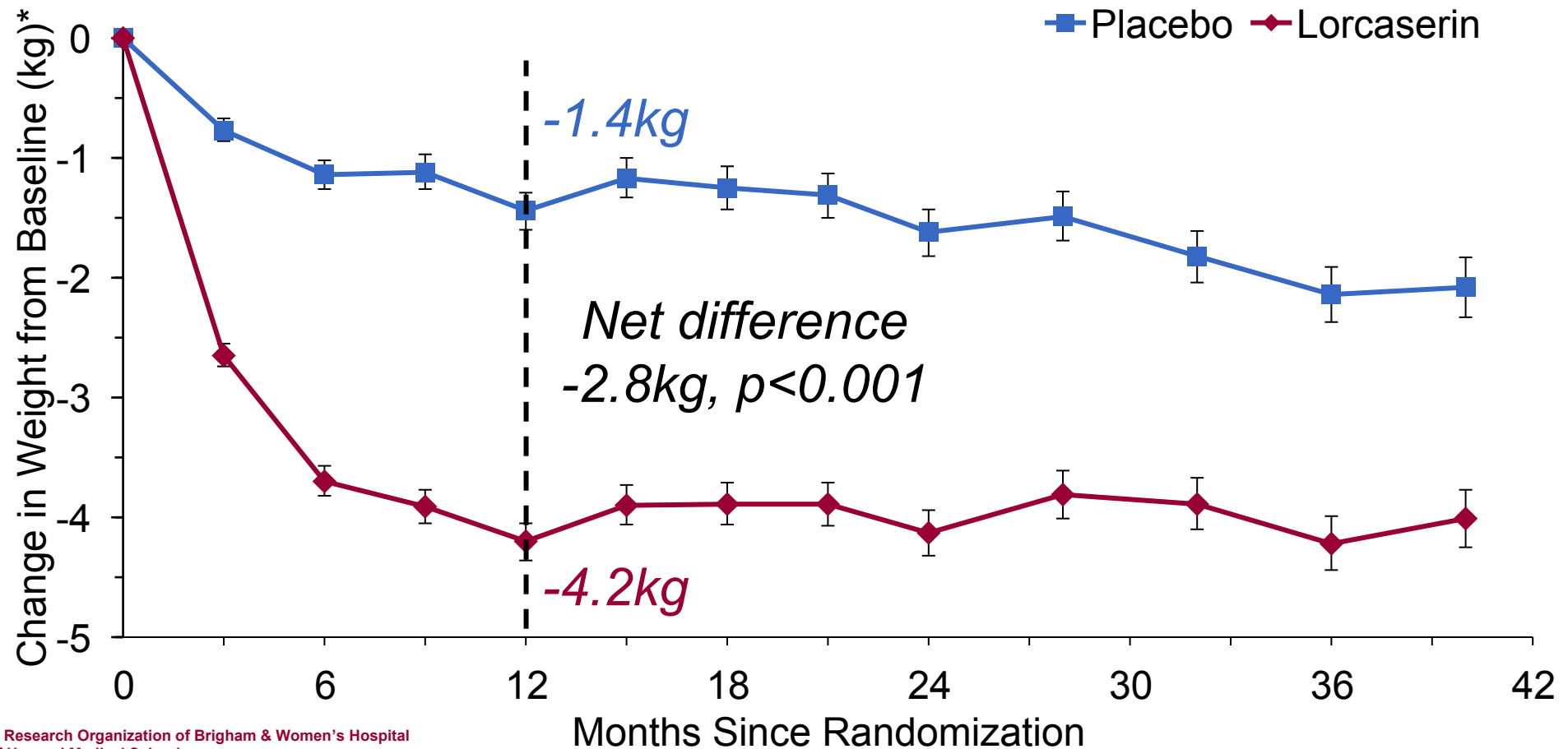
Pooled data; no differences between treatment arms

Median Follow-up: 3.3 yrs

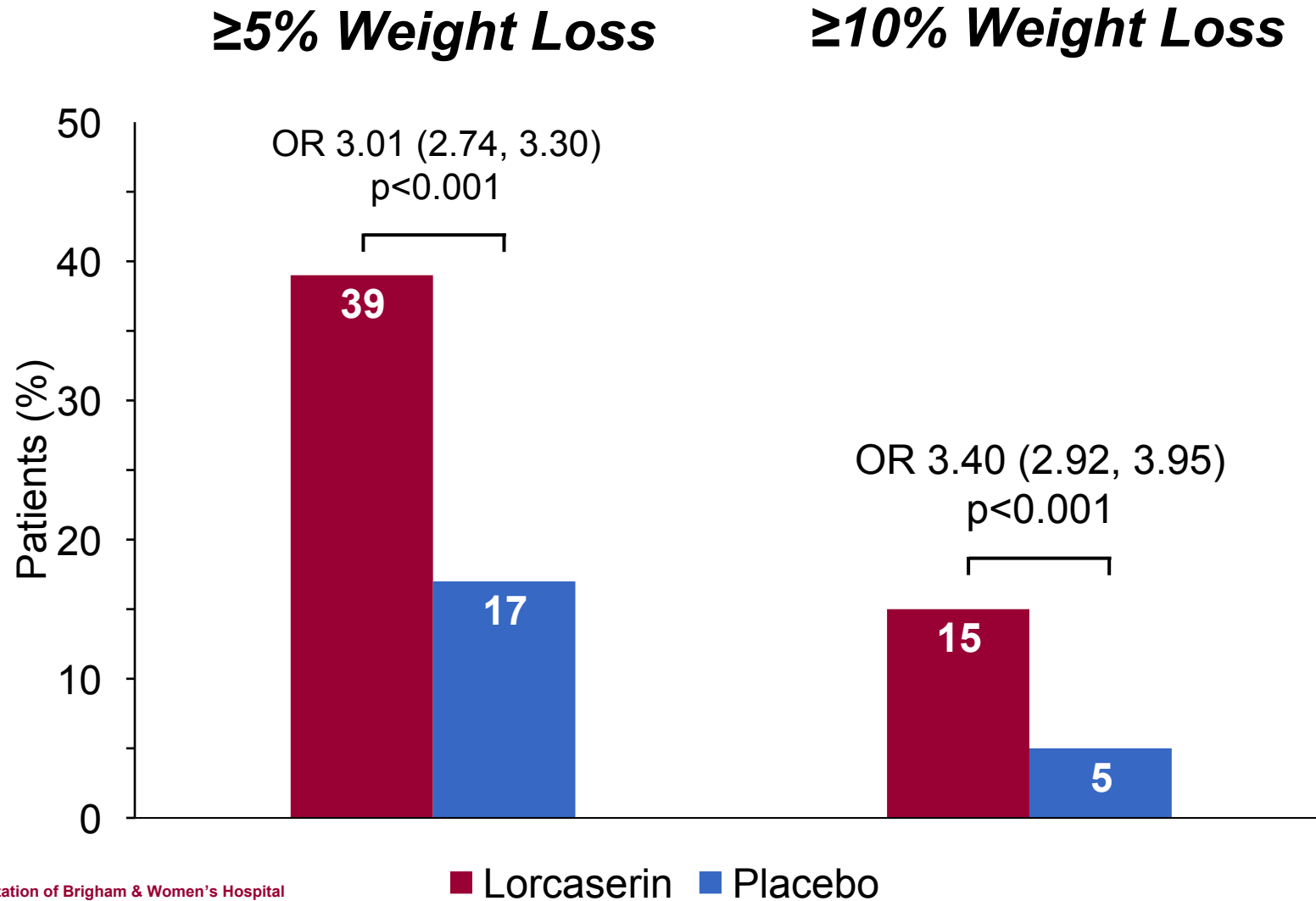
	Lorcaserin N=6,000	Placebo N=6,000
Study Drug Discontinuation, %/yr	12.0	12.7
Lost-to-follow-up, %/yr	0.2	0.3
Withdrawal of Consent, %/yr	0.6	0.7
Completed Study*, %	98	97

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

On a background of lifestyle interventions:



Weight Loss at 1 Year



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

Primary CV Outcomes

N = 12,000

**CV Death, MI, Stroke
(Safety)**

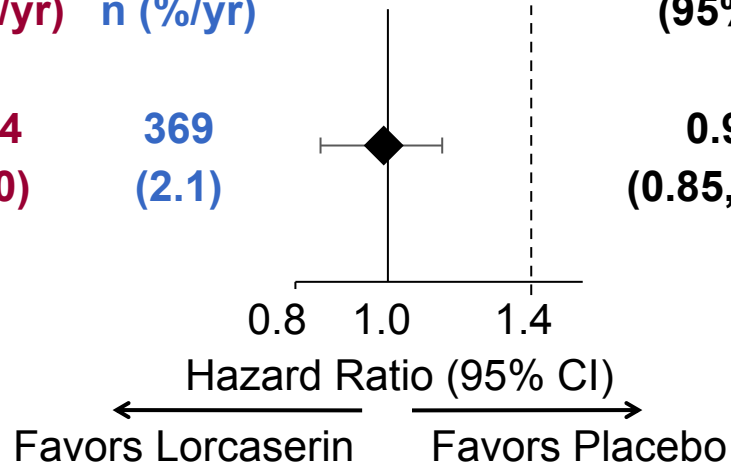
Lorc **Pbo**
n (%/yr) **n (%/yr)**

**CV death,
MI, or stroke**

**364
(2.0)** **369
(2.1)**

**MACE HR
(95%CI)**

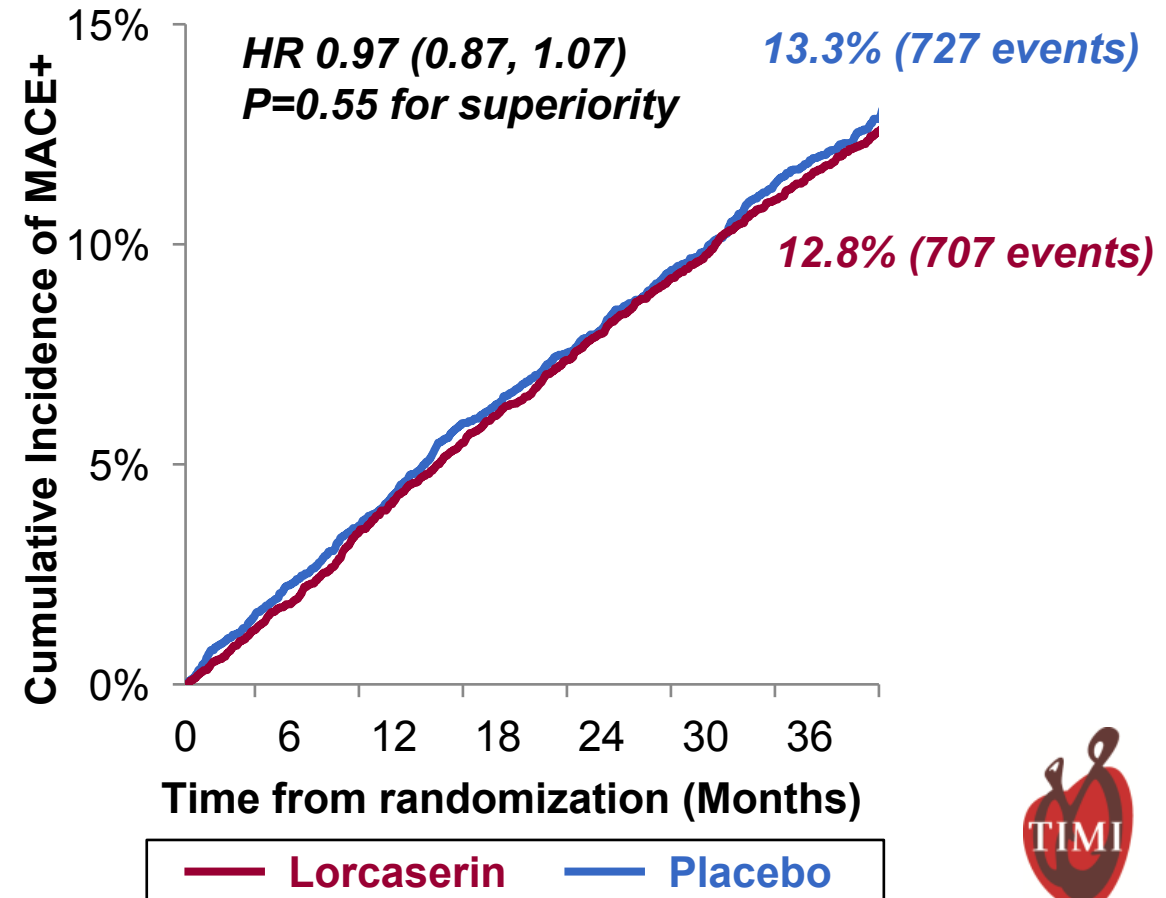
**0.99*
(0.85, 1.14)**



***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)**



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

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*

	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*

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)***

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.

ORIGINAL ARTICLE

Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients

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