

Effect of Lorcaserin on Prevention and Remission of Type 2 Diabetes in CAMELLIA-TIMI 61, a randomized trial in overweight and obese patients

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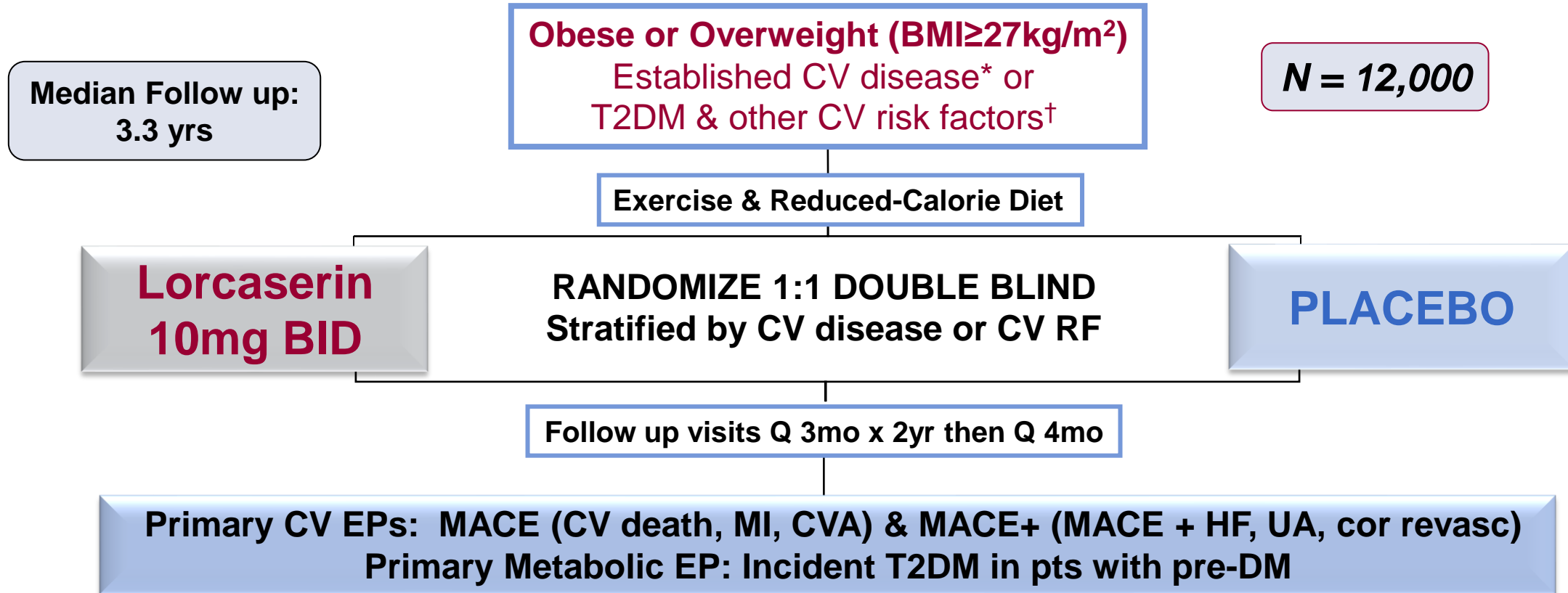
- Grants from Eisai, during the conduct of the study
- Grants from AstraZenaca, Novartis, and Merck
- Personal fees from AstraZeneca, Biogen Idec, Boehringer Ingelheim, Covance, Dr Reddy's Laboratory, Eisai, Elsevier Practice Update Cardiology, GlaxoSmithKline, Merck, NovoNordisk, Sanofi, and St Jude's Medical; and other support from Health [at] Scale, outside of the the study.

- Obesity is associated with development and progression of impaired glucose tolerance and T2DM in pts without DM, and worsening glycemic control among pts with T2DM
- Weight loss agents are guideline-recommended adjuncts to lifestyle modification for chronic weight management^{1, 2}
- Predominantly short-term studies of weight loss agents have demonstrated improvements in glycemic parameters, but long-term data are limited.

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

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

Trial Schema



*CAD, PAD or cerebrovascular disease; [†]T2DM with ≥ 1 of following: HTN, HL, hsCRP > 3, eGFR 30-60, albuminuria

On a background of lifestyle modification in obese or overweight pts at high CV risk, to assess the effect of lorcaserin vs placebo by glycemic subgroups on:

- Weight
- Glycemic parameters, incl. HbA1c & FPG
- Glucose-lowering agent (GLA) utilization
- Glycemic outcomes
 - Prevention of incident DM in pre-DM (primary EP) or no DM (secondary EP)
 - Remission of diabetes
- Diabetic Microvascular Complications
 - Nephropathy (albuminuria), neuropathy, retinopathy
- Safety - Hypoglycemia

- **Incident diabetes – Adjudicated by a blinded TIMI clinical events committee, according to ADA definitions:**
 - $\text{RPG} \geq 200$ mg/dL & symptoms of hyperglycemia or
 - $\text{HbA1c} \geq 6.5\%$, $\text{FPG} \geq 126$ mg/dL or 2 hr OGTT glucose ≥ 200 mg/dL with confirmation on consecutive or simultaneous testing or med initiation
- **Remission of diabetes**
 - Remission of hyperglycemia ($\text{HbA1c} < 6.5$, $\text{FPG} < 126$, no meds) in pts with DM
 - Achievement of normoglycemia ($\text{HbA1c} < 5.7$, $\text{FPG} < 100$, no meds) in pts with pre-DM and/or DM
 - For both outcomes:
 - Persistent = maintained through follow up
 - Sustained = maintained for ≥ 2 measurements ≥ 30 d apart
 - Any = achieved at any time

Baseline Characteristics

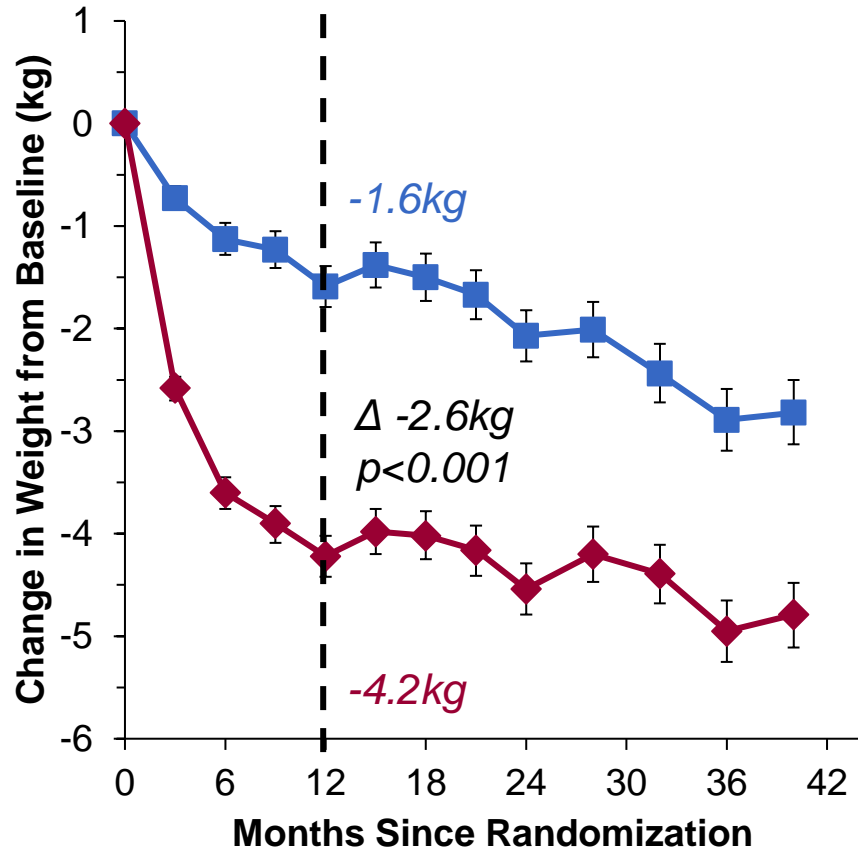
Characteristic	Diabetes (N=6816, 57%)	Pre-diabetes (N=3991, 33%)	Normoglycemia (N=1193, 10%)
Age (median)	64	64	62
Male, %	60	72	64
Weight in kg (median)	105	100	96
BMI in kg/m ² (median)	36	34	33
Multiple CV Risk Factor, %	45	0	0
Established CV Disease, %	55	100	100
Coronary artery disease	50	92	88
Peripheral arterial disease	5	6	7
Cerebrovascular disease	9	10	11
Hypertension, %	94	87	82
Hyperlipidemia, %	94	93	90
eGFR < 60 ml/min/1.73m ² , %	23	15	15

Pooled data; no differences between treatment arms

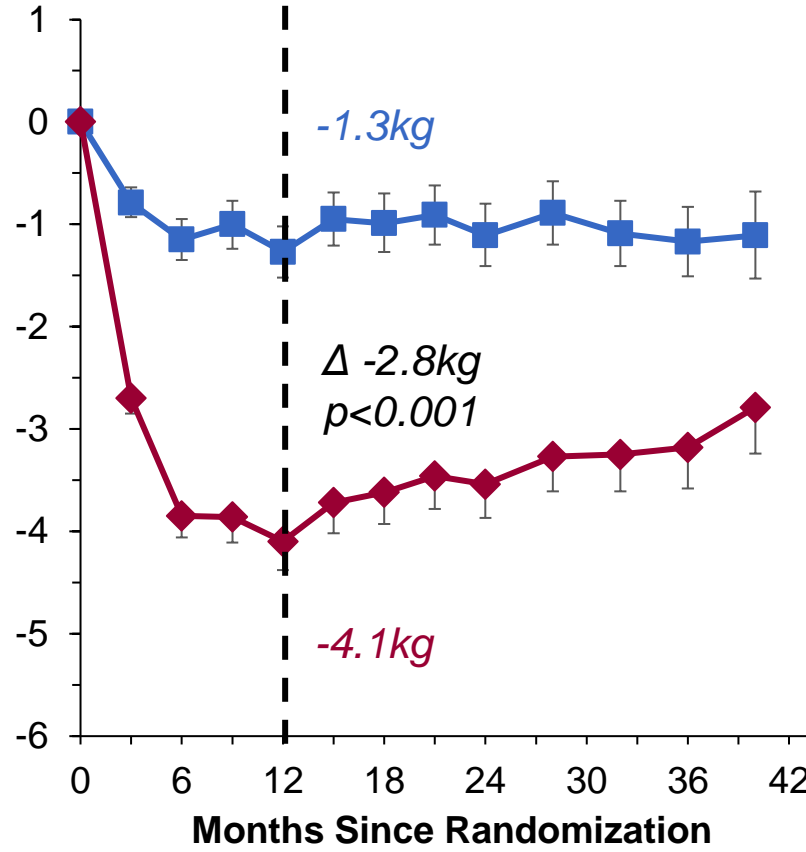
*Diabetes = investigator-reported hx of DM, any HbA1c ≥ 6.5%, FPG ≥ 126mg/dL or glucose-lowering meds;
pre-DM = no DM, any HbA1c ≥ 5.7-<6.5%, FPG ≥ 100-<126mg/dL; normoglycemia = no DM or pre-DM*

Weight Loss

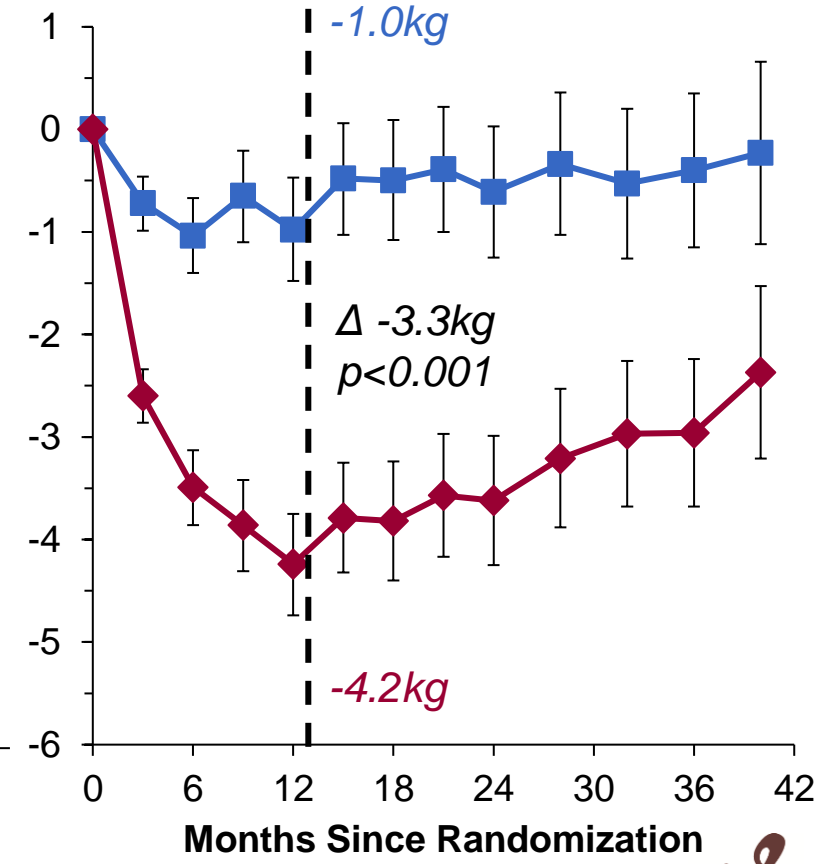
Pts w/ Diabetes



Pts w/ Pre-Diabetes

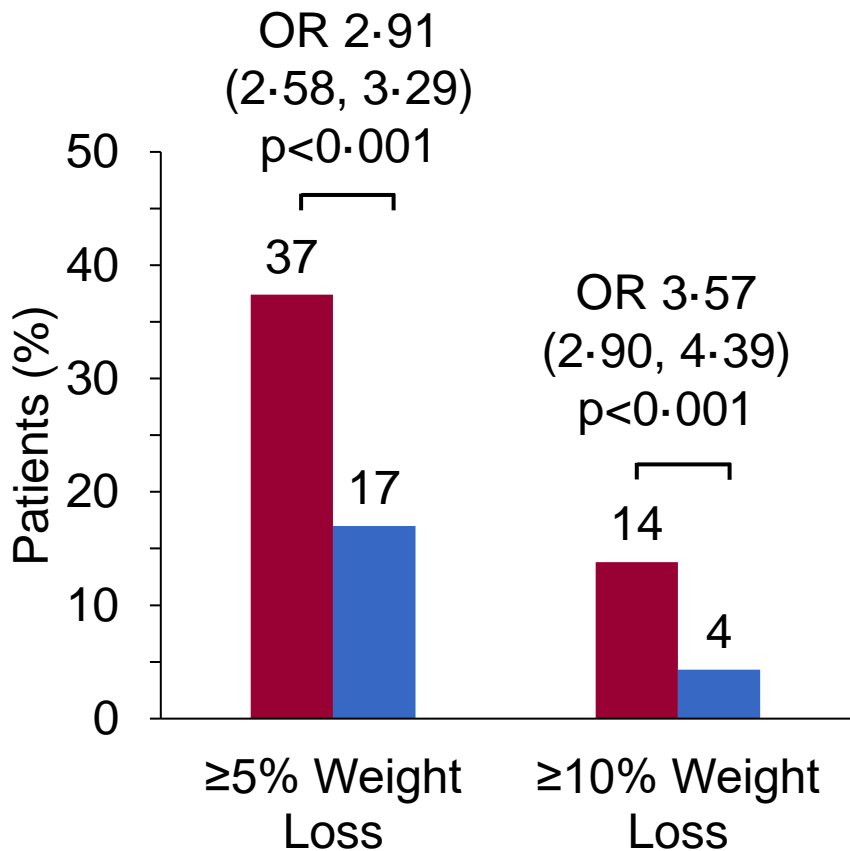


Pts w/ Normoglycemia

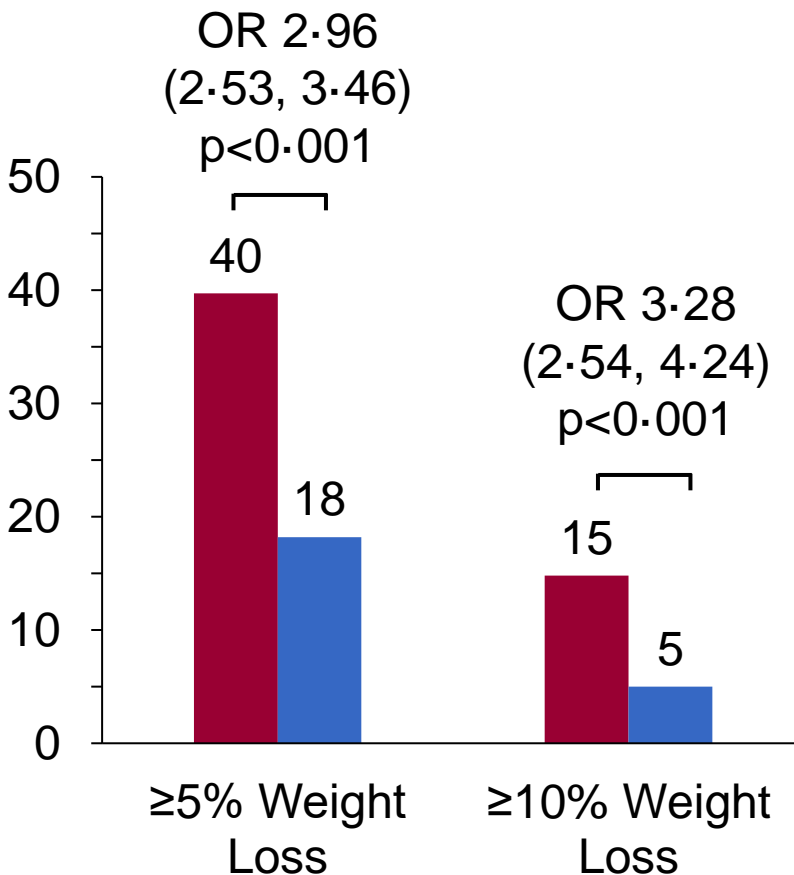


Weight Loss of $\geq 5\%$ or $\geq 10\%$

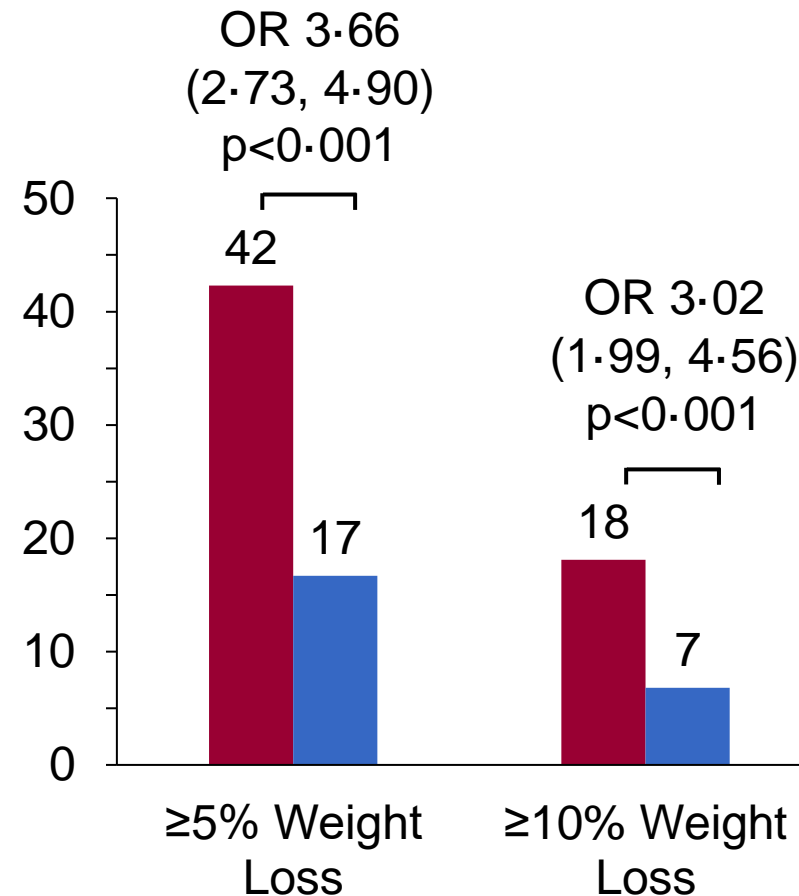
Pts w/ Diabetes



Pts w/ Pre-Diabetes

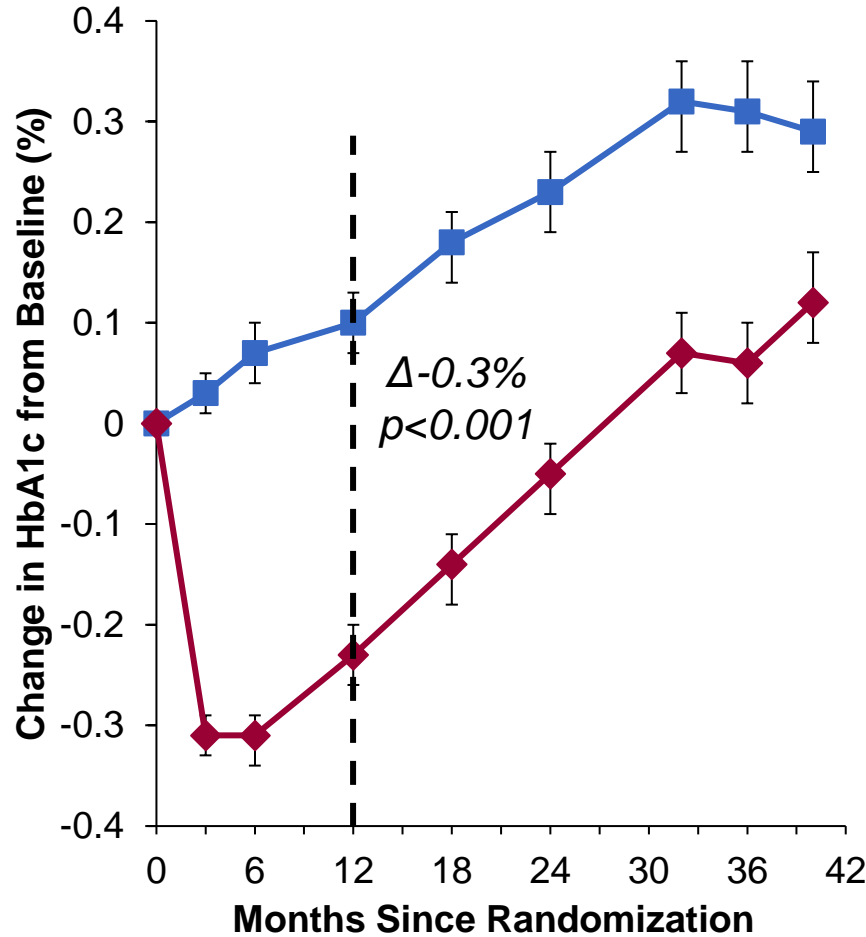


Pts w/ Normoglycemia

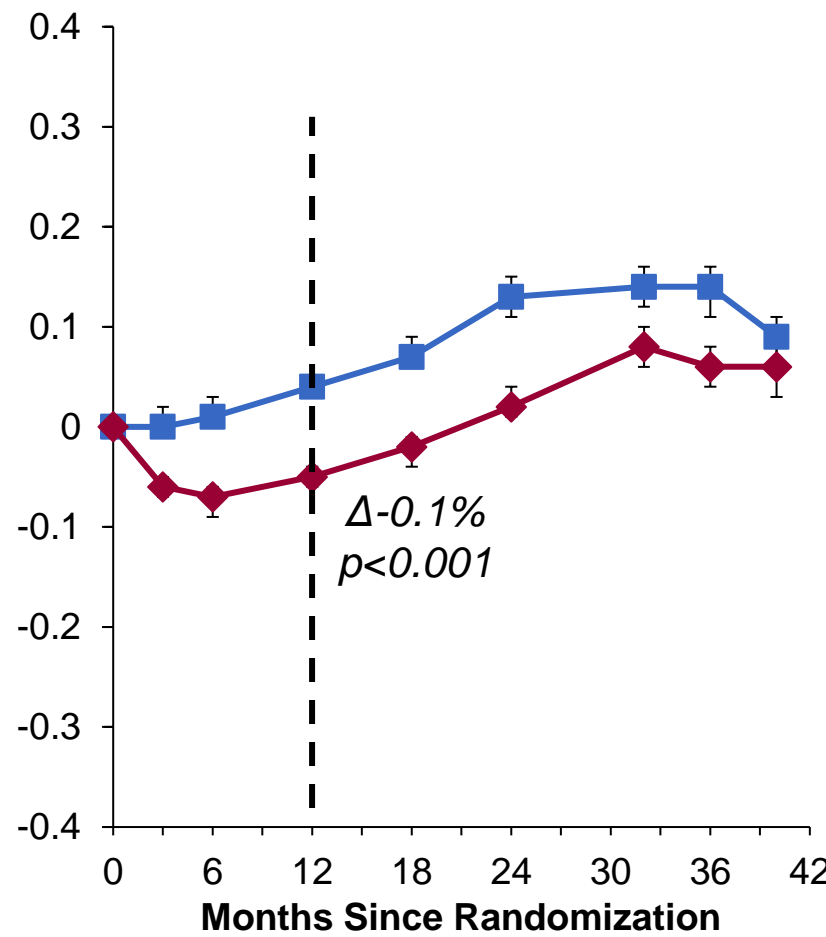


Hemoglobin A1c

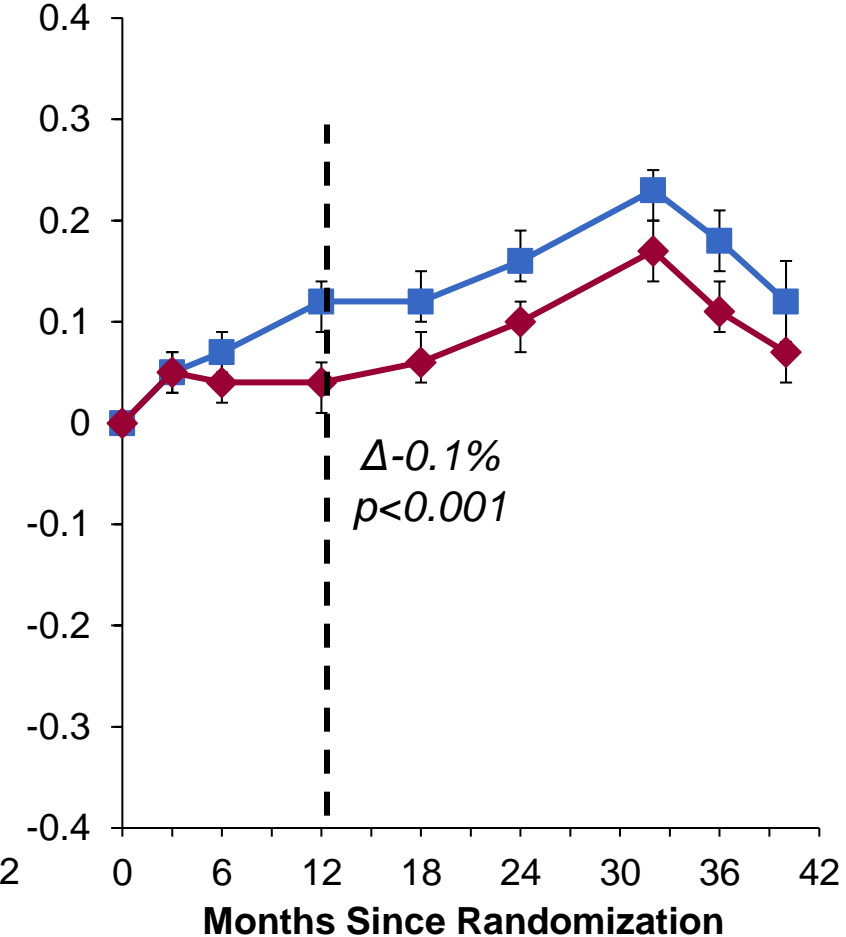
Pts w/ Diabetes



Pts w/ Pre-Diabetes



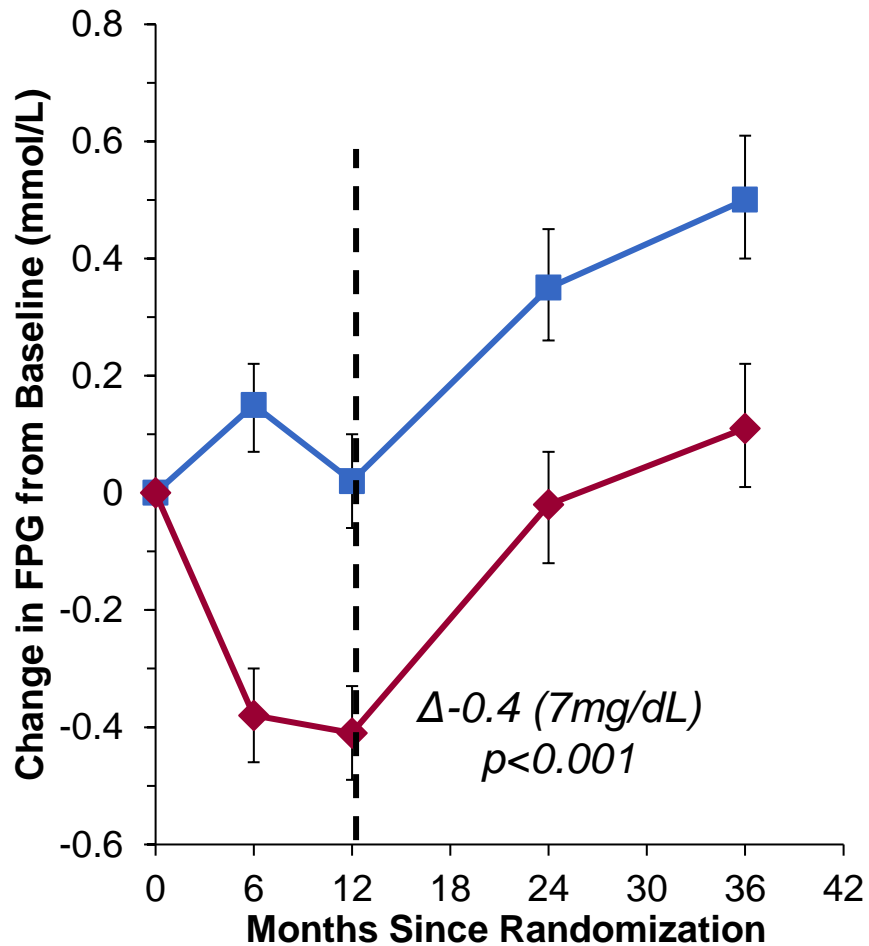
Pts w/ Normoglycemia



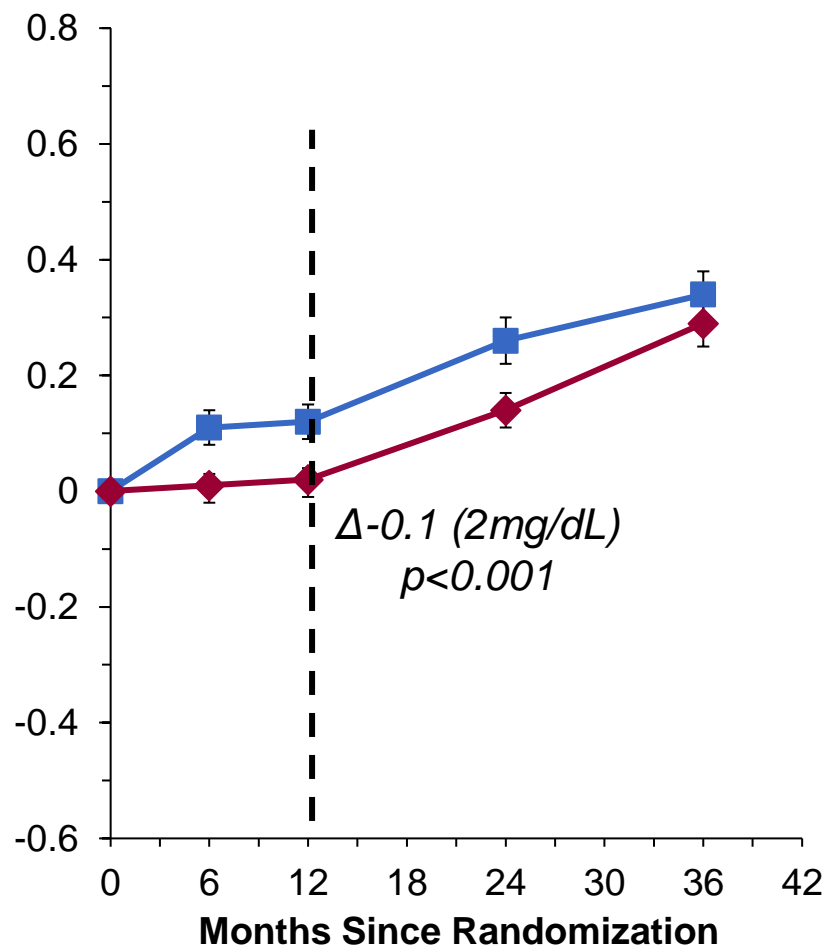
■ Lorcaserin ■ Placebo

Fasting Plasma Glucose

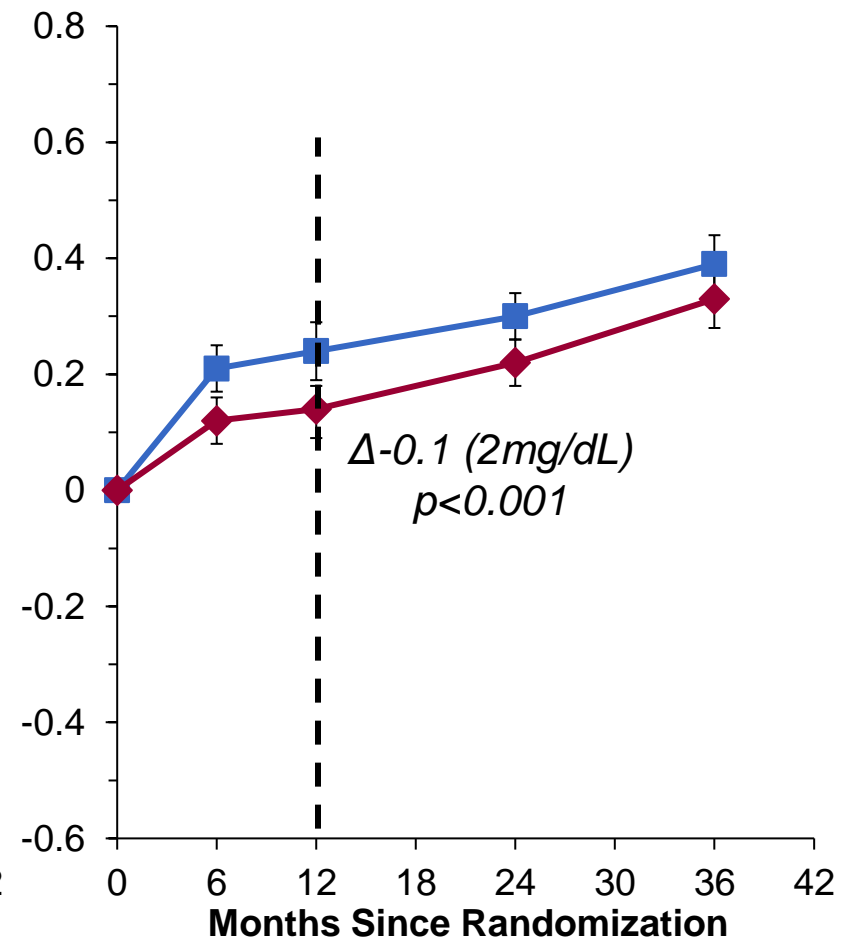
Pts w/ Diabetes



Pts w/ Pre-Diabetes

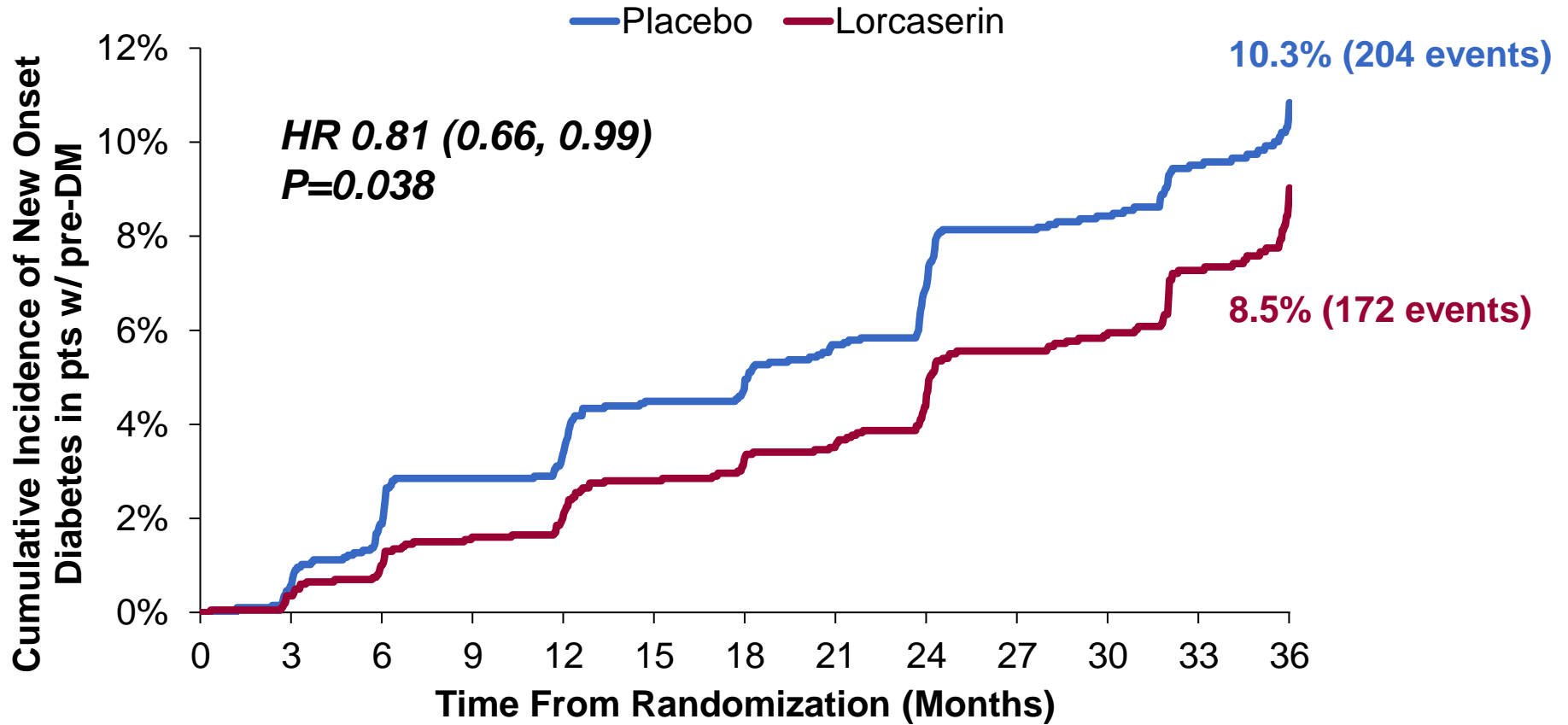


Pts w/ Normoglycemia



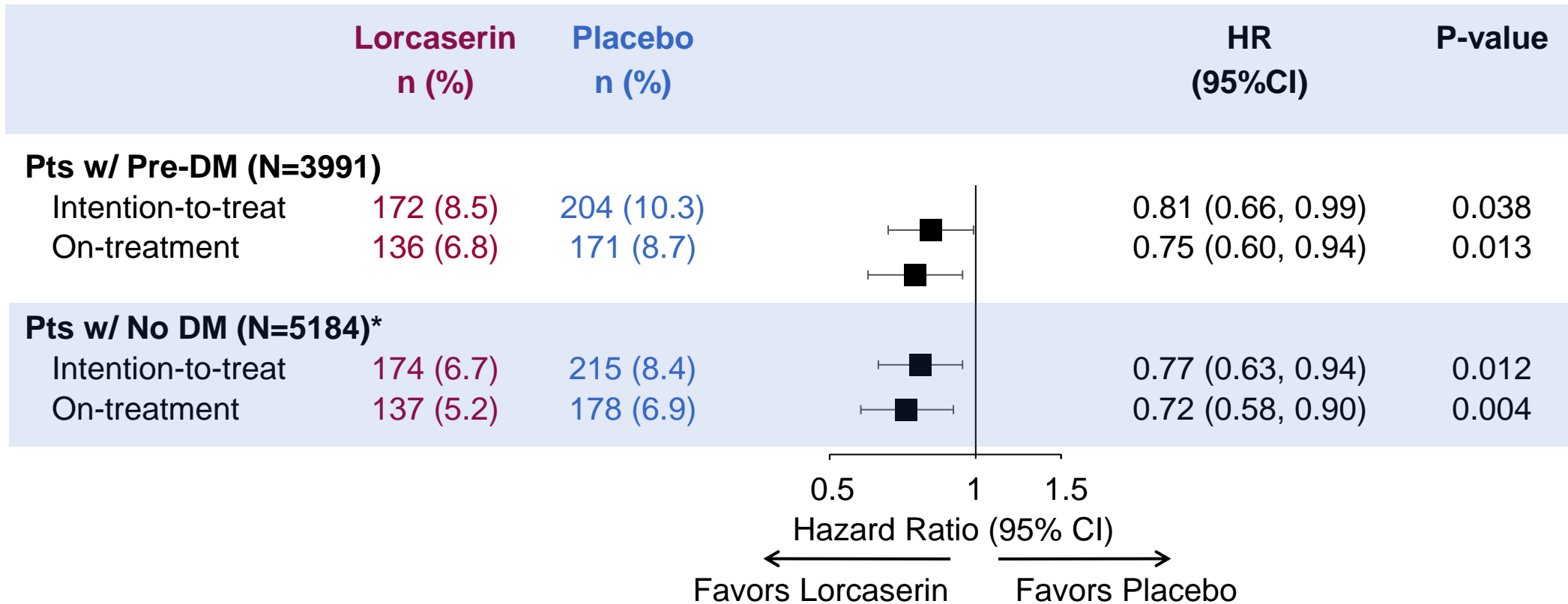
■ Lorcaserin ■ Placebo

Incident Diabetes



Placebo	1976	1883	1784	826
Lorcaserin	2015	1950	1872	890

Adjudicated by a blinded clinical events committee according to ADA definition



Adjudicated by a blinded clinical events committee according to ADA definition

**Pts with pre-DM or normoglycemia at baseline*

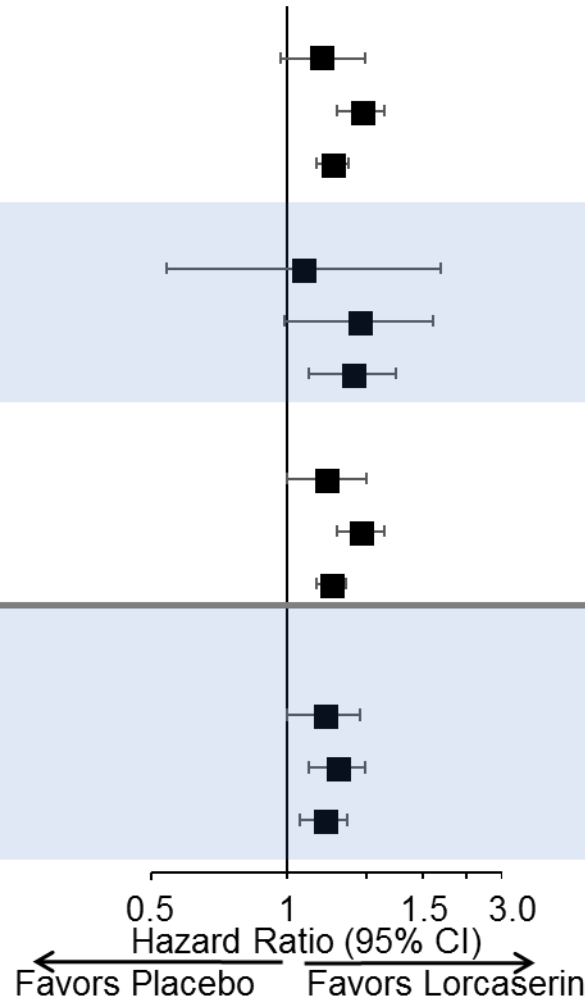
Glucose-Lowering Agents

Pts w/ Diabetes	Lorcaserin %	Placebo %	RR (95% CI)	p-value
New GLA at 1 Year	13.1	20.1	0.65 (0.58, 0.73)	<0.0001
New insulin	1.6	3.9	0.41 (0.29, 0.60)	<0.0001
New non-insulin	12.3	18.1	0.68 (0.60, 0.76)	<0.0001
Stopped GLA at 1 Year	10.1	7.9	1.28 (1.08, 1.51)	0.005
Stopped insulin	4.5	2.9	1.57 (0.98, 2.50)	0.058
Stopped non-insulin	9.8	8.1	1.20 (1.01, 1.44)	0.041

GLA, glucose-lowering agent
Event rate (%) = n/N at 1 year

Remission of Diabetes

	Lorcaserin %	Placebo %	HR (95%CI)	P-value
Achievement of Normoglycemia				
<i>Pre-Diabetes (N=3991)</i>				
Persistent	9.2	7.6	1.20 (0.97, 1.49)	0.093
Sustained	29.8	21.6	1.46 (1.29, 1.65)	<0.001
Any	59.9	51.9	1.26 (1.16, 1.37)	<0.001
<i>Diabetes (N=6816)</i>				
Persistent	0.5	0.4	1.08 (0.54, 2.19)	0.82
Sustained	1.9	1.3	1.44 (0.99, 2.11)	0.057
Any	5.6	4.1	1.40 (1.12, 1.74)	0.0027
<i>Diabetes and Pre-Diabetes (N=10807)</i>				
Persistent	3.7	3.1	1.22 (1.00, 1.50)	0.055
Sustained	12.3	8.7	1.45 (1.29, 1.64)	<0.0001
Any	25.9	21.5	1.25 (1.16, 1.35)	<0.0001
Remission of Hyperglycemia				
<i>Diabetes (N=6816)</i>				
Persistent	7.1	6.0	1.21 (1.00, 1.45)	0.049
Sustained	12.7	10.0	1.29 (1.12, 1.49)	0.0004
Any	16.3	13.7	1.21 (1.07, 1.36)	0.0029





Camellia Microvascular Complications

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

Pts w/ Diabetes at Baseline	Lorcaserin % N=3385	Placebo % N=3431	HR (95% CI)	p-value
Microvascular composite	10.1	12.4	0.79 (0.69, 0.92)	0.001
Persistent microalbuminuria	7.8	10.0	0.77 (0.66, 0.90)	0.001
Diabetic retinopathy	0.7	0.9	0.84 (0.50, 1.43)	0.53
Diabetic neuropathy	1.9	2.0	0.94 (0.67, 1.32)	0.71

Event rate (%) = n/N over duration of follow up.

Persistent microalbuminuria defined by new microalbuminuria (Urine albumin-creatinine-ratio \geq 30mg/g) on 2 consecutive assessments at least 30 days apart

	Lorcaserin %	Placebo %	p-value
Pts w/ diabetes at baseline	N=3383	N=3427	
Any	6.6	5.8	0.18
Mild	2.8	2.6	0.65
Moderate	2.9	2.7	0.60
Severe	0.6	0.4	0.38
Severe with serious complications*	0.4	0.1	0.054
Pts w/ diabetes at baseline on insulin or sulfonylurea	N=1633	N=1634	
Any	12.0	10.5	0.18
Mild	4.6	4.2	0.63
Moderate	5.5	5.3	0.78
Severe	1.2	0.7	0.21
Severe with serious complications*	0.7	0.2	0.054
Pts w/ diabetes at baseline	N=2612	N=2565	
Any	0.3	0.1	0.10

Event rate (%) = n/N in the safety population during the on-treatment period over duration of follow up, reported as the most severe event on a per pt basis. *Severe hypoglycemia with serious complications is defined by hospitalization or life-threatening injury.

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

- ***Resulted in modest, durable weight loss in all glycemic subgroups***
- ***Decreased incident diabetes in pts with preDM or no DM***
- ***Tended to increase achievement of normoglycemia in pts with preDM or DM***
- ***Increased remission of hyperglycemia in pts with DM***
- ***Reduced the risk of diabetic microvascular complications***

Taken together, these findings reinforce the notion that modest, durable weight loss can improve cardiometabolic health and supports the role of lorcaserin as an adjunct to lifestyle modification for chronic management of weight and metabolic health.

THE LANCET

Effect of lorcaserin on prevention and remission of type 2 diabetes in overweight and obese patients (CAMELLIA-TIMI 61): a randomised, placebo-controlled trial

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