

Lipid-Modulating Effects of Evacetrapib, a Novel CETP Inhibitor, Administered as Monotherapy or in Combination with the Most Commonly-Used Statins

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Disclosures

- Research support: AstraZeneca, Anthera, Eli Lilly, Novartis, Resverlogix, Roche and LipoScience
- Consulting and honoraria: AstraZeneca, Eli Lilly, Anthera, Omthera, Merck, Takeda, Resverlogix, Sanofi-Aventis, CSL Behring, Esperion, Boehringer Ingelheim
- The study was sponsored by Eli Lilly

Steering Committee

- Steven Nissen (Chair)
- Stephen Nicholls (Principal Investigator)
- Bryan Brewer
- John Kastelein
- Holger Schilske (non-voting)

Background

- Cholesteryl ester transfer protein (CETP) inhibition represents a potentially useful strategy to raise HDL-C and lower LDL-C.
- Despite the failure of torcetrapib, interest in CETP inhibitors remains strong.
- Evacetrapib is a novel CETP inhibitor without adverse effects on blood pressure or mineralocorticoid activity in preclinical studies.
- The lipid effects of evacetrapib in combination with statins and in dyslipidemia remain unknown.

Objective

To characterize the efficacy, safety and tolerability of evacetrapib as monotherapy and in combination with commonly-used statins in patients with low HDL-C or high LDL-C

Study Design

- Subjects with elevated LDL-C or low HDL-C
- Up to 8 week dietary lead-in period and withdrawal of lipid-modifying therapies
- 12 week treatment period
 - Evacetrapib (30, 100 or 500 mg) or placebo
 - Evacetrapib 100 mg or placebo in combination with statin therapy (simvastatin 40 mg, atorvastatin 20 mg, rosuvastatin 10 mg)
- Co-primary endpoints: Percent change in HDL-C and LDL-C

1154 patients screened at 70 centers in US and Europe

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graph TD; A[1154 patients screened at 70 centers in US and Europe] --> B[826 patients entered dietary lead-in period and withdrawal of lipid-modifying therapies]; B --> C[398 patients randomized to treatment groups]; C --> D[393 patients received study drug]; D --> E[382 patients with follow up lipid data for primary analysis];
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826 patients entered dietary lead-in period and withdrawal of lipid-modifying therapies

398 patients randomized to treatment groups

393 patients received study drug

382 patients with follow up lipid data for primary analysis

Demographic Characteristics

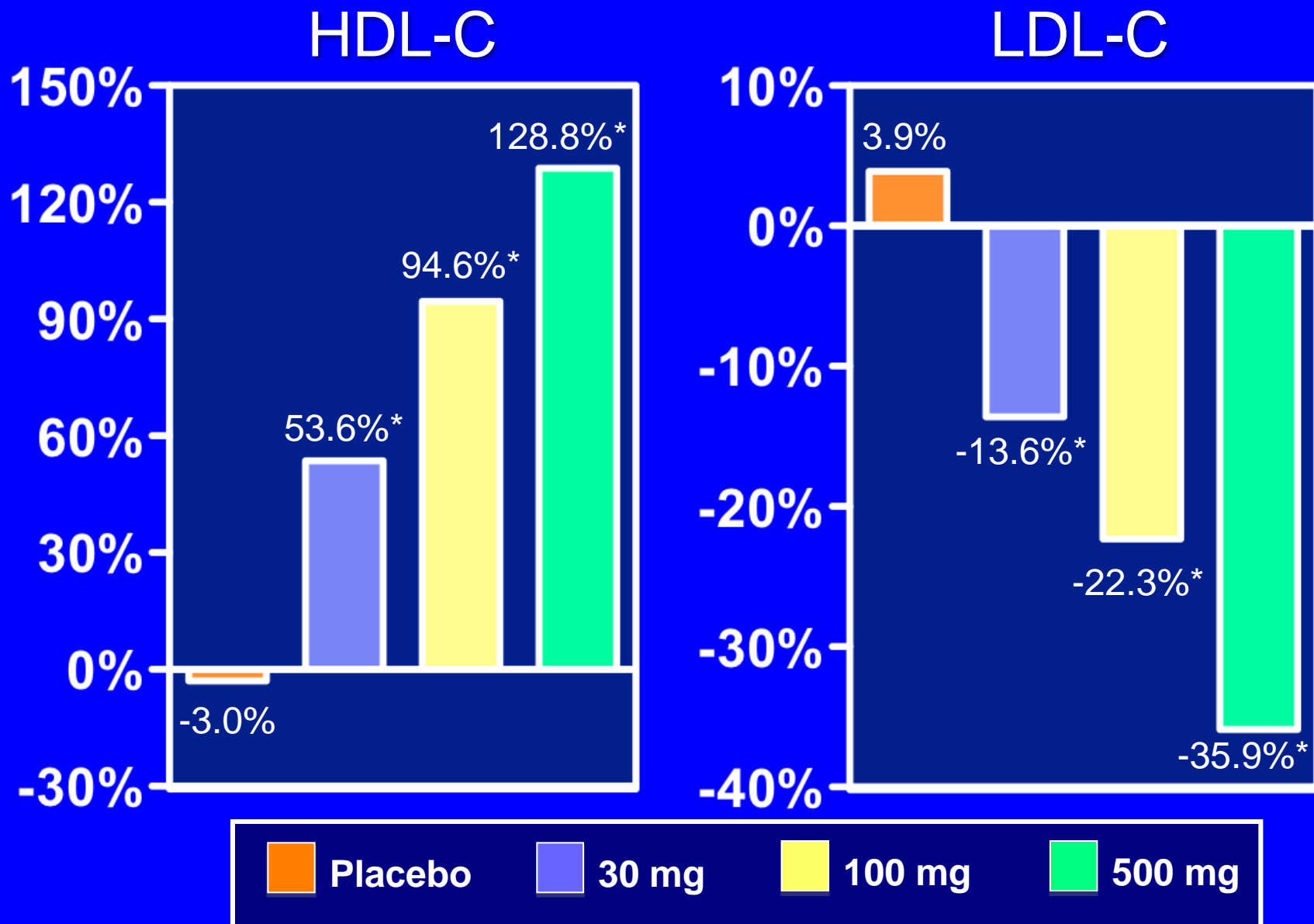
Parameter	Cohort (n=393)
Mean age (years)	58.3
Females	56%
Mean body mass index (kg/m ²)	29.0
Metabolic Syndrome	25.7%
History of Hypertension	35.1%
Diabetes	4.1%
Smoker	14.8%
Mean systolic BP (mmHg)	122.8
Mean diastolic BP (mmHg)	77.5

Baseline Characteristics

Parameter	Cohort (n=393)
LDL-C (mg/dL)	144.3
HDL-C (mg/dL)	55.1
Triglycerides (mg/dL)*	121.3
Non-HDL C (mg/dL)	170.7
ApoB (mg/dL)	107.1
ApoA-I (mg/dL)	156.8
ApoA-II (mg/dL)	39.3
hsCRP (mg/L)*	1.5

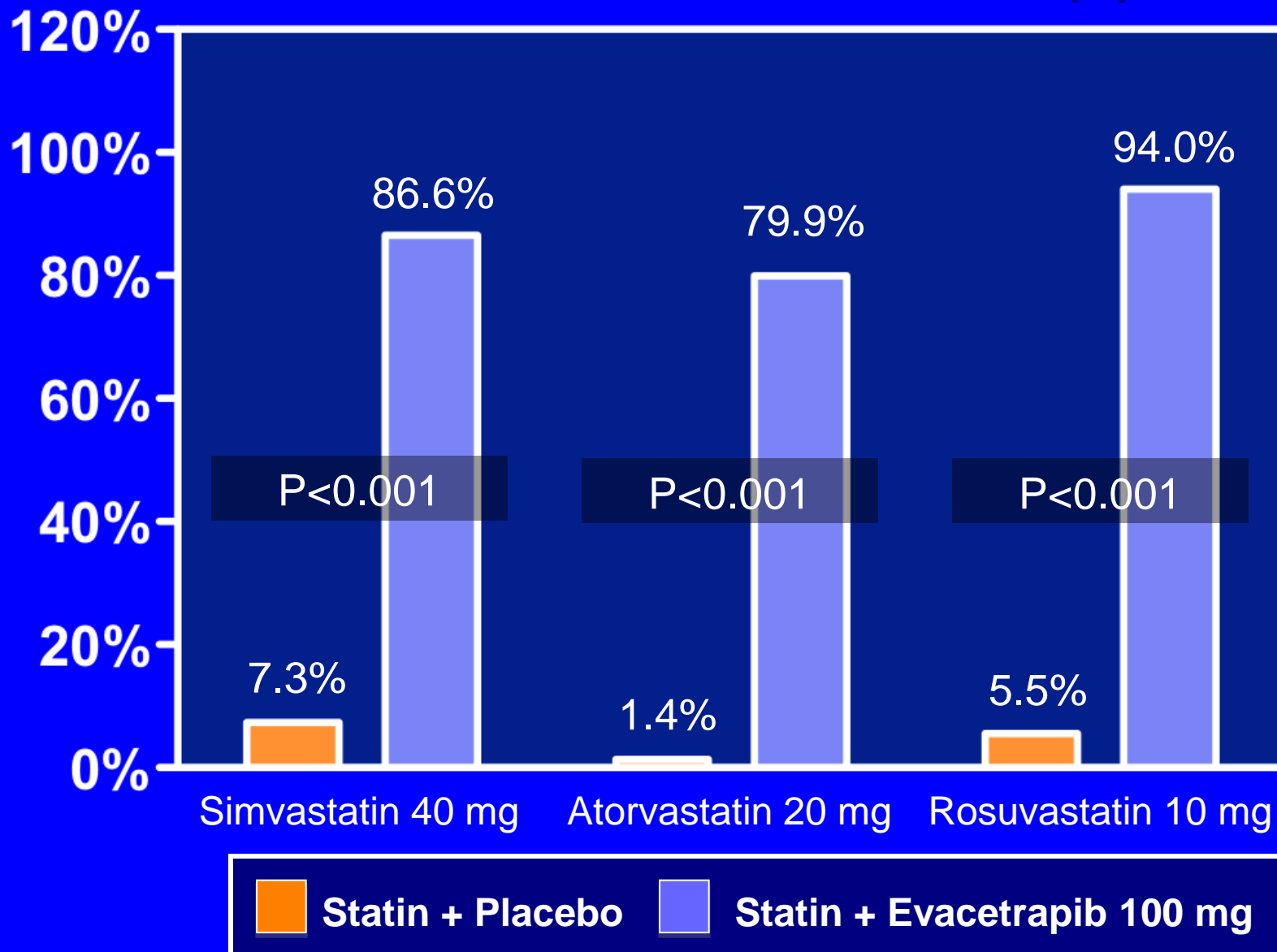
Presented as mean values. *median values

Percent Changes in HDL-C and LDL-C

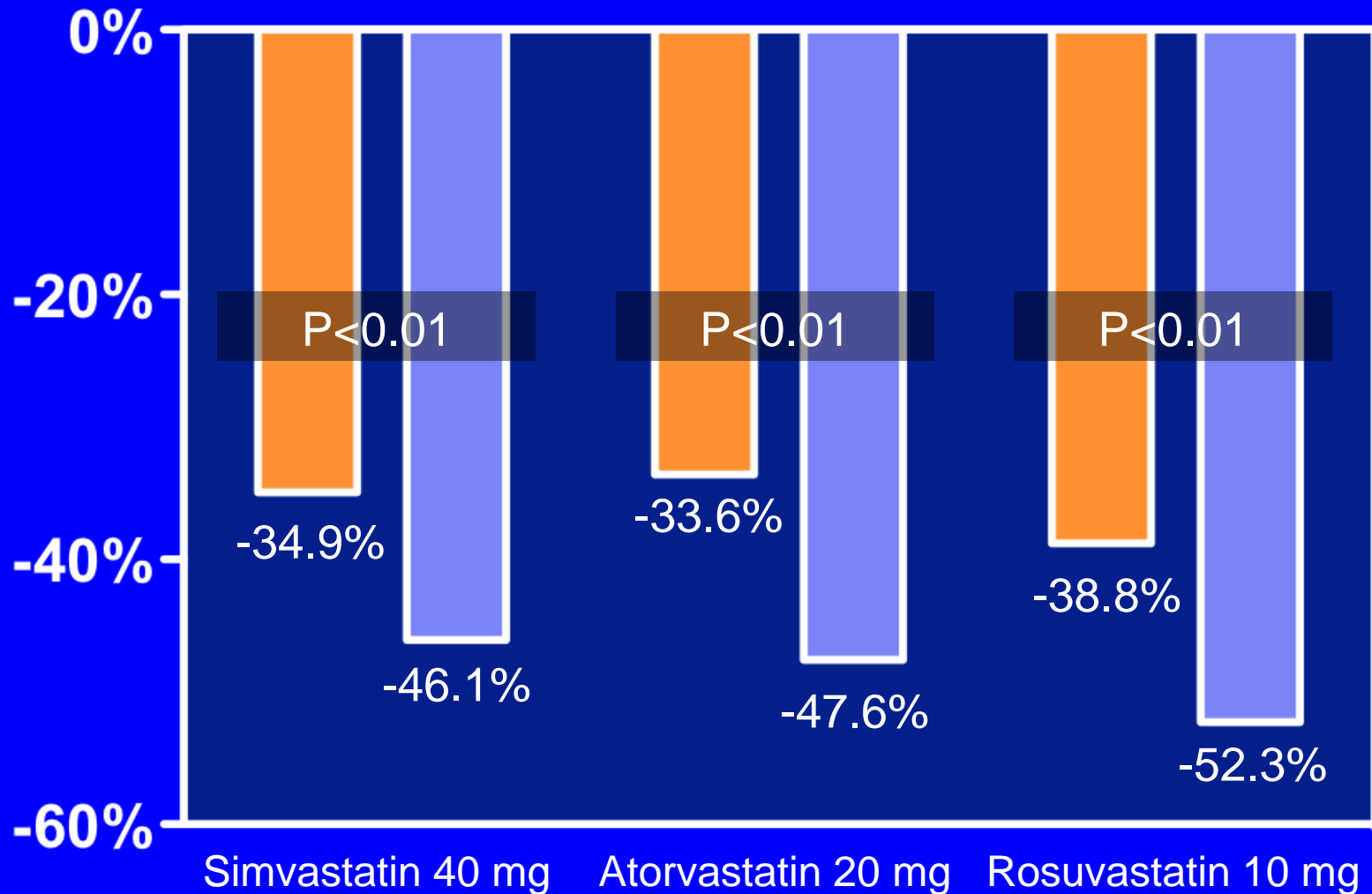



* P<0.001 compared with placebo

Percent Change HDL-C: Evacetrapib 100 mg Combined with Statin Therapy



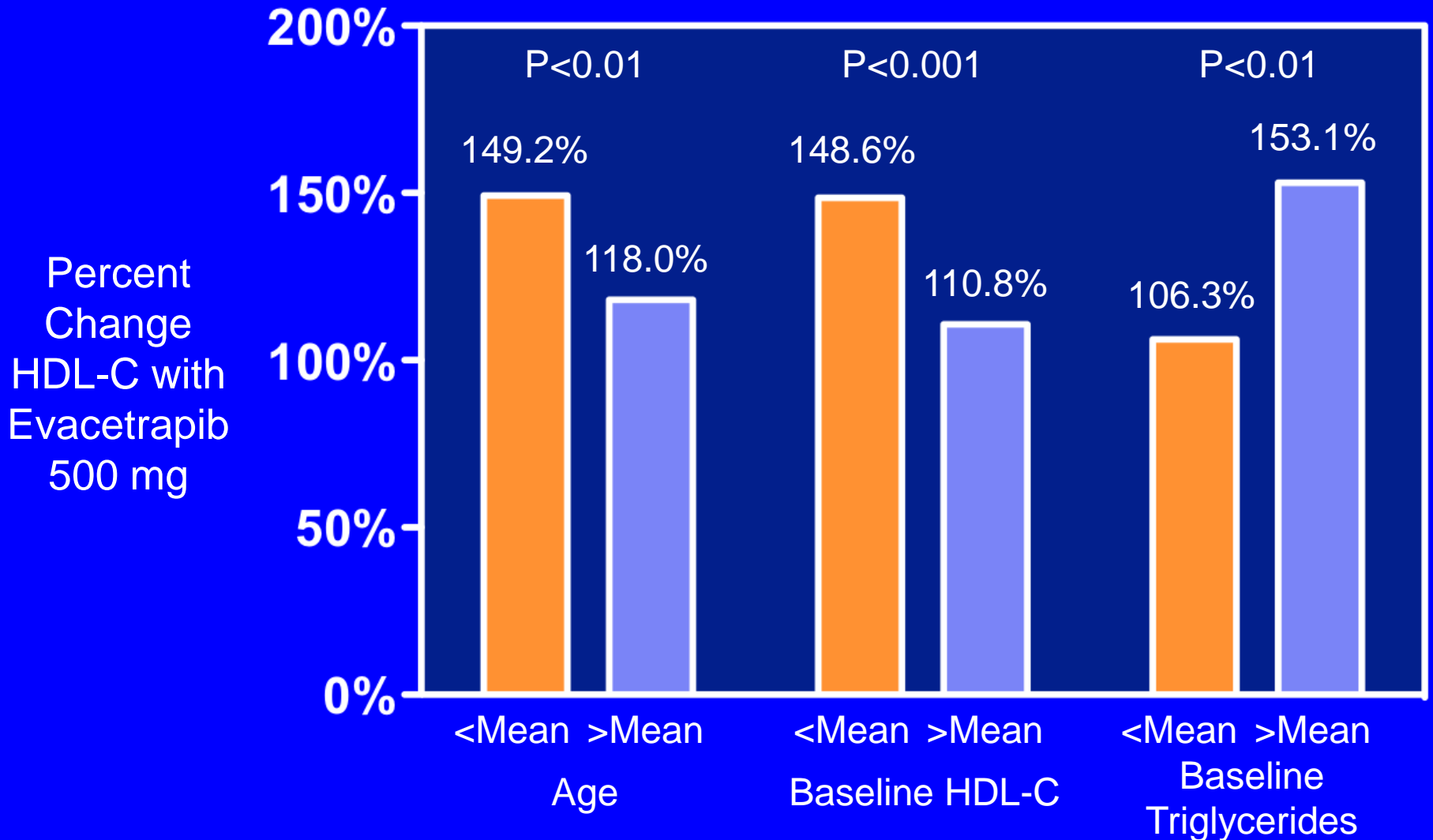
Percent Change LDL-C: Evacetrapib 100 mg Combined with Statin Therapy



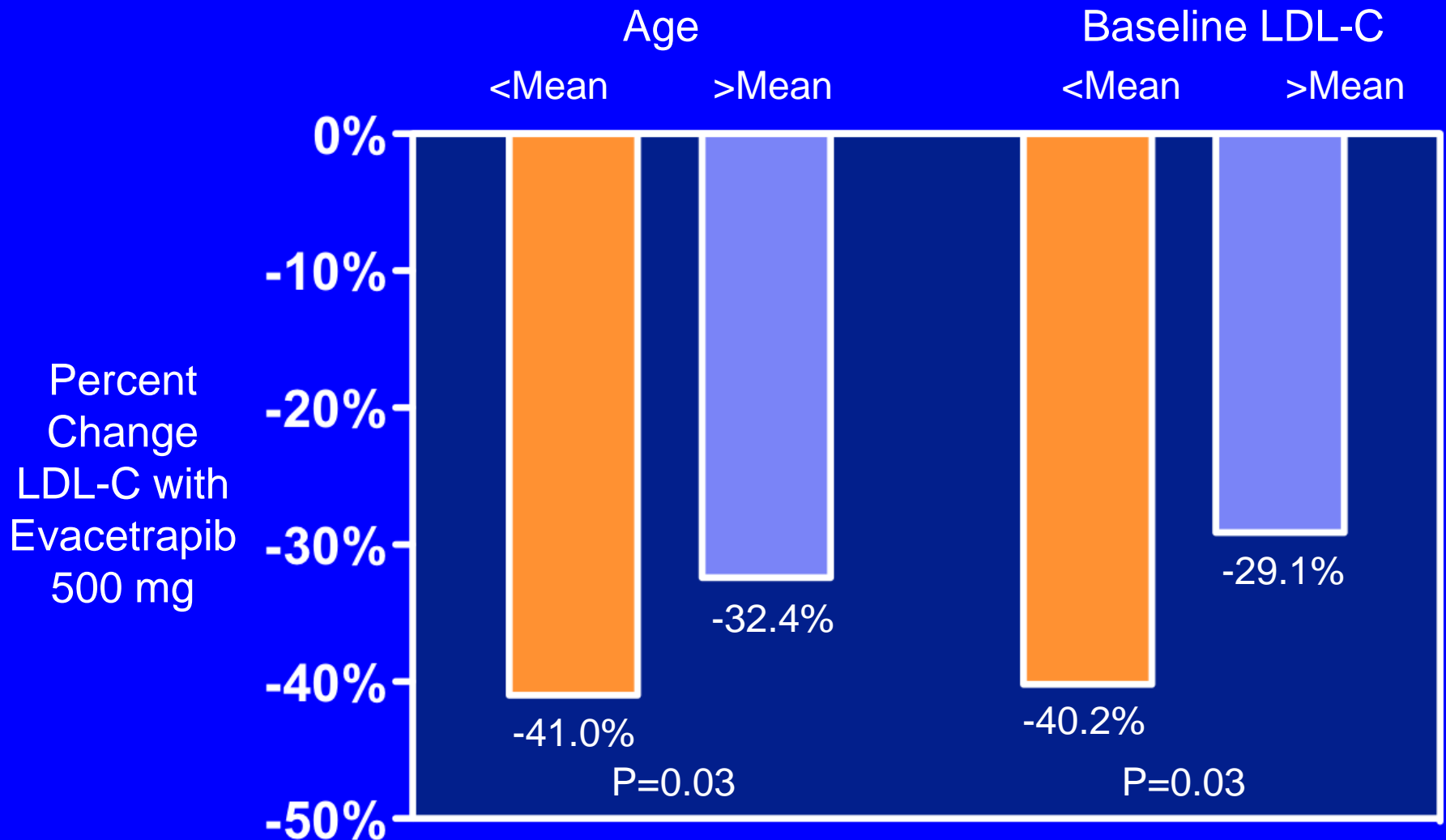
 **Statin + Placebo**

 **Statin + Evacetrapib 100 mg**

Subgroup Heterogeneity: Percent Change HDL-C with Evacetrapib

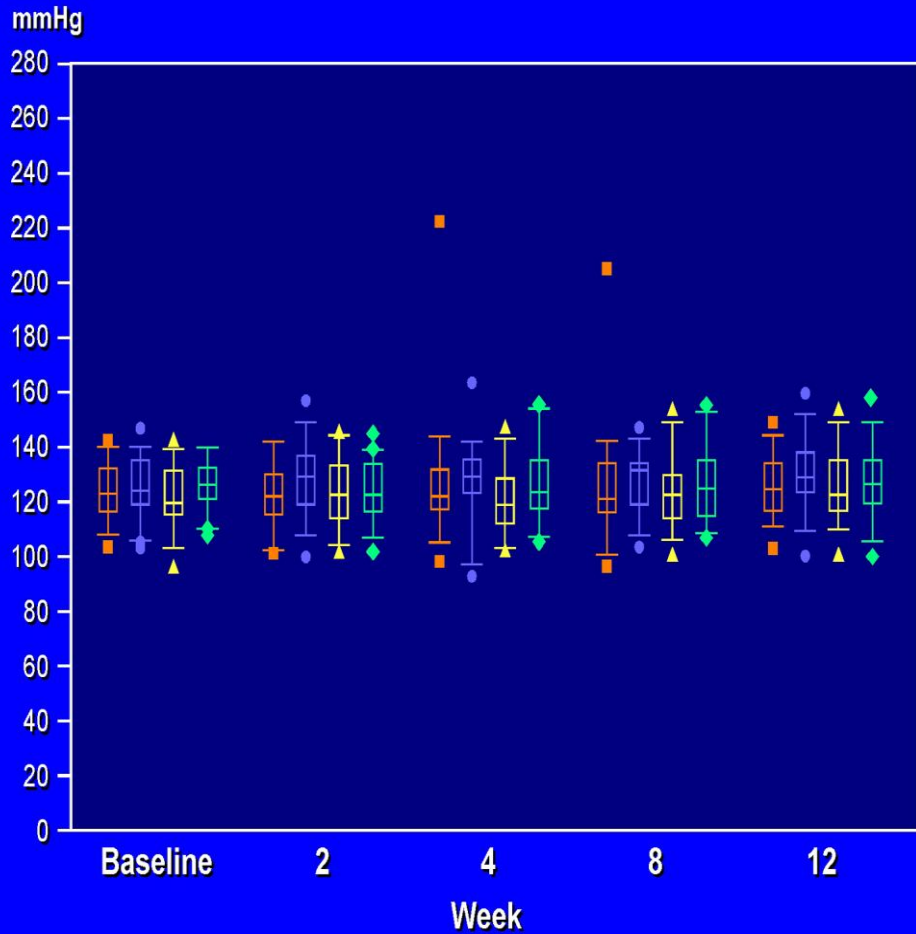


Subgroup Heterogeneity: Percent Change LDL-C with Evacetrapib

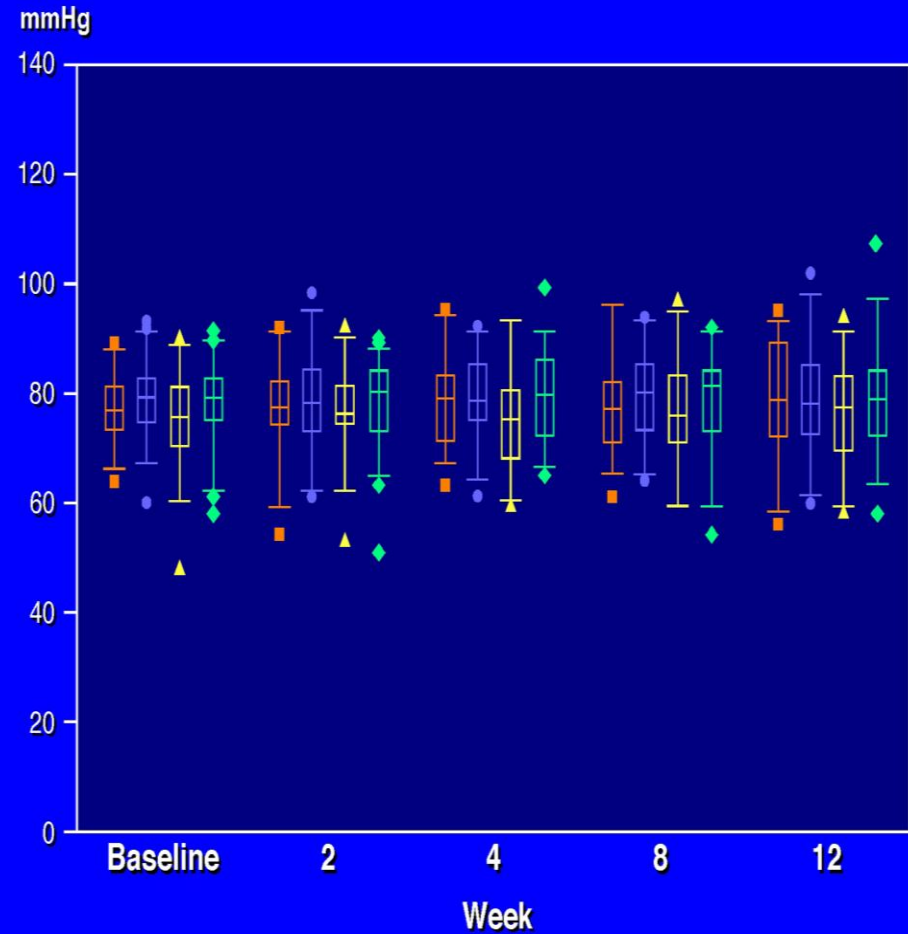


Blood Pressure

Systolic Blood Pressure



Diastolic Blood Pressure



Safety Evaluation

Parameter	Placebo (n=38)	Eva 30 mg (n=40)	Eva 100 mg (n=38)	Eva 500 mg (n=40)	Statin (n=121)	Statin + Eva 100 mg (n=116)
Drug-related AE	18.4%	20.0%	13.2%	25.0%	18.2%	26.7%
AE leading to discontinuation	2.6%	5.0%	2.6%	12.5%	2.5%	7.8%
SAE	0.0%	0.0%	0.0%	2.5%	0.8%	1.7%
Creatinine >ULN	2.6%	2.6%	5.2%	10.0%	7.6%	5.2%
CK > 5 X ULN	2.6%	0.0%	0.0%	0.0%	1.7%	1.7%
ALT > 3 X ULN	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%
Aldosterone (ng/dL)*	-1.00	-0.45	0.96	-0.30	-1.12	-0.45
Salivary Cortisol (µg/dL)*	-0.003	-0.03	0.002	0.004	0.03	0.01

* Absolute change

Conclusions

- Evacetrapib monotherapy produced a dose-dependent increase in HDL-C up to 128.8% and decrease in LDL-C up to 35.9%.
- Significant incremental HDL-C and LDL-C changes were observed when evacetrapib 100 mg was administered in combination with statins.
- Evacetrapib was well tolerated with no evidence of adverse blood pressure or mineralocorticoid effects.
- The impact of evacetrapib on cardiovascular events remains to be determined.

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Video Interview

Effects of the CETP Inhibitor Evacetrapib Administered as Monotherapy or in Combination With Statins on HDL and LDL Cholesterol

A Randomized Controlled Trial

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THE DEVELOPMENT OF STATINS for reducing low-density lipoprotein cholesterol (LDL-C) has revolutionized cardiovascular disease prevention.¹⁻⁶ Nonetheless, cardiovascular disease remains the number one cause of death.⁷ Accordingly, considerable efforts have focused on development of novel therapeutic agents designed to address residual cardiovascular risk. Because individuals from the general population with elevations of high-density lipoprotein cholesterol (HDL-C) have a reduced incidence of coronary heart disease,⁸ it has been assumed that finding an appropriate therapy to increase HDL-C levels would yield substantial clinical benefit.

However, development of drugs that increase HDL-C levels has been challenging and fraught with failures, including the premature termination of

Context Interest remains high in cholesteryl ester transfer protein (CETP) inhibitors as cardioprotective agents. Few studies have documented the efficacy and safety of CETP inhibitors in combination with commonly used statins.

Objective To examine the biochemical effects, safety, and tolerability of evacetrapib, as monotherapy and in combination with statins, in patients with dyslipidemia.

Design, Setting, and Participants Randomized controlled trial conducted among 398 patients with elevated low-density lipoprotein cholesterol (LDL-C) or low high-density lipoprotein cholesterol (HDL-C) levels from April 2010 to January 2011 at community and academic centers in the United States and Europe.

Interventions Following dietary lead-in, patients were randomly assigned to receive placebo (n=38); evacetrapib monotherapy, 30 mg/d (n=40), 100 mg/d (n=39), or 500 mg/d (n=42); or statin therapy (n=239) (simvastatin, 40 mg/d; atorvastatin, 20 mg/d; or rosuvastatin, 10 mg/d) with or without evacetrapib, 100 mg/d, for 12 weeks.

Main Outcome Measures The co-primary end points were percentage changes from baseline in HDL-C and LDL-C after 12 weeks of treatment.

Results The mean baseline HDL-C level was 55.1 (SD, 15.3) mg/dL and the mean baseline LDL-C level was 144.3 (SD, 26.6) mg/dL. As monotherapy, evacetrapib produced dose-dependent increases in HDL-C of 30.0 to 66.0 mg/dL (53.6% to 128.8%) compared with a decrease with placebo of -0.7 mg/dL (-3.0%; $P < .001$ for all compared with placebo) and decreases in LDL-C of -20.5 to -51.4 mg/dL (-13.6% to -35.9%) compared with an increase with placebo of 7.2 mg/dL (3.9%; $P < .001$ for all compared with placebo). In combination with statin therapy, evacetrapib, 100 mg/d, produced increases in HDL-C of 42.1 to 50.5 mg/dL (78.5% to 88.5%; $P < .001$ for all compared with statin monotherapy) and decreases in LDL-C of -67.1 to -75.8 mg/dL (-11.2% to -13.9%; $P < .001$ for all compared with statin monotherapy). Compared with evacetrapib monotherapy, the combination of statins and evacetrapib resulted in greater reductions in LDL-C ($P < .001$) but no greater increase in HDL-C ($P = .39$). Although the study was underpowered, no adverse effects were observed.

Conclusions Compared with placebo or statin monotherapy, evacetrapib as monotherapy or in combination with statins increased HDL-C levels and decreased LDL-C levels. The effects on cardiovascular outcomes require further investigation.

Trial Registration clinicaltrials.gov Identifier: NCT01105975

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For editorial comment see p 2153.

Author Video Interview available at www.jama.com.

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A Final Thought

- Substantial HDL-C raising, and with some agents incremental LDL-C lowering, has stimulated interest in the development of CETP inhibitors.
- Elucidating the off-target toxicities of torcetrapib has provided hope that CETP inhibition will be shown to be a cardioprotective strategy.
- Ultimately large cardiovascular outcome trials will determine whether CETP inhibitors will reduce the residual risk observed despite the use of existing therapies.