The CLEAR Outcomes Trial

Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen

Steven E. Nissen MD MACC

On behalf of the CLEAR investigators and our extraordinary patients

Study Sponsor:
Esperion Therapeutics, Inc.

C5Research

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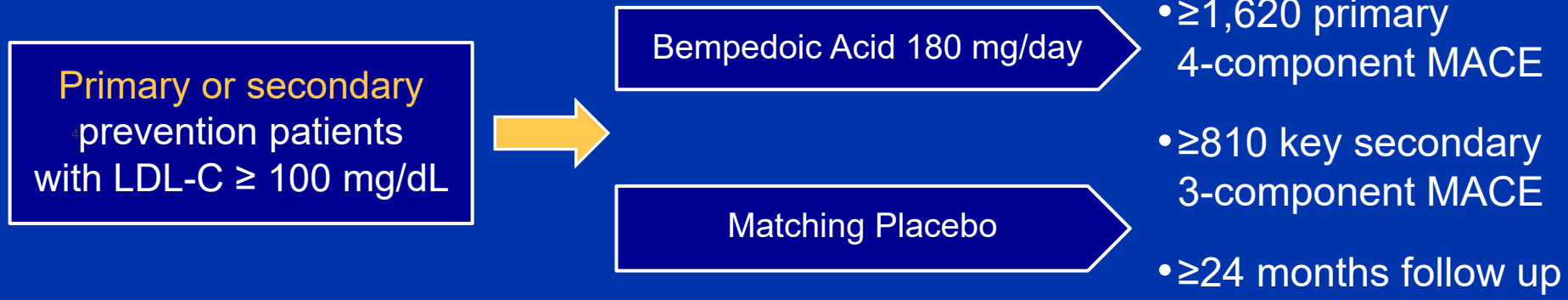
Background

- Statin intolerance is a vexing problem that prevents many patients from achieving LDL-C levels associated with cardiovascular benefits.
- Bempedoic acid, an ATP citrate lyase inhibitor, inhibits hepatic cholesterol synthesis upstream of HMG-Co-A reductase, the enzyme inhibited by statins.
- Bempedoic acid is a pro-drug activated in the liver, but not peripheral tissues, resulting in a low incidence of muscle-related adverse events.
- Although approved for lowering LDL-C, the effects of bempedoic acid on cardiovascular outcomes has not been assessed .

CLEAR Outcomes Trial Design

- Statin intolerance: An adverse effect that started or increased during statin therapy and resolved or improved after therapy discontinued.
- Intolerance to 2 or more statins or 1 statin if unwilling to attempt a second statin or advised by physician to not attempt second statin. Very low dose statin therapy permitted (< lowest approved dose).



Statin Intolerance Confirmation Form

- Patient must confirm and sign:
  - "…I can't tolerate these medications (called statins) even though I know they would reduce my risk of a heart attack or stroke or death. My doctor has explained and I am aware that many patients who are unable to tolerate a single statin medication may also be able to tolerate a different statin or dose."
- Signed provider statement:
  - "…in my opinion, this patient is unable to tolerate statin therapy (except possibly at very low average daily doses)….based on my review of the medical and medication histories and discussion with the patient."

Primary and Key Secondary Endpoints

- Primary endpoint 4-component MACE: nonfatal MI, nonfatal stroke, coronary revascularization or cardiovascular death
- Hierarchical testing of key secondary endpoints:

1) 3-component MACE (MI, stroke or CV death)
2) Fatal and nonfatal MI
3) Coronary revascularization
4) Fatal and nonfatal stroke
5) Cardiovascular death
6) All-cause mortality

Sequential Testing

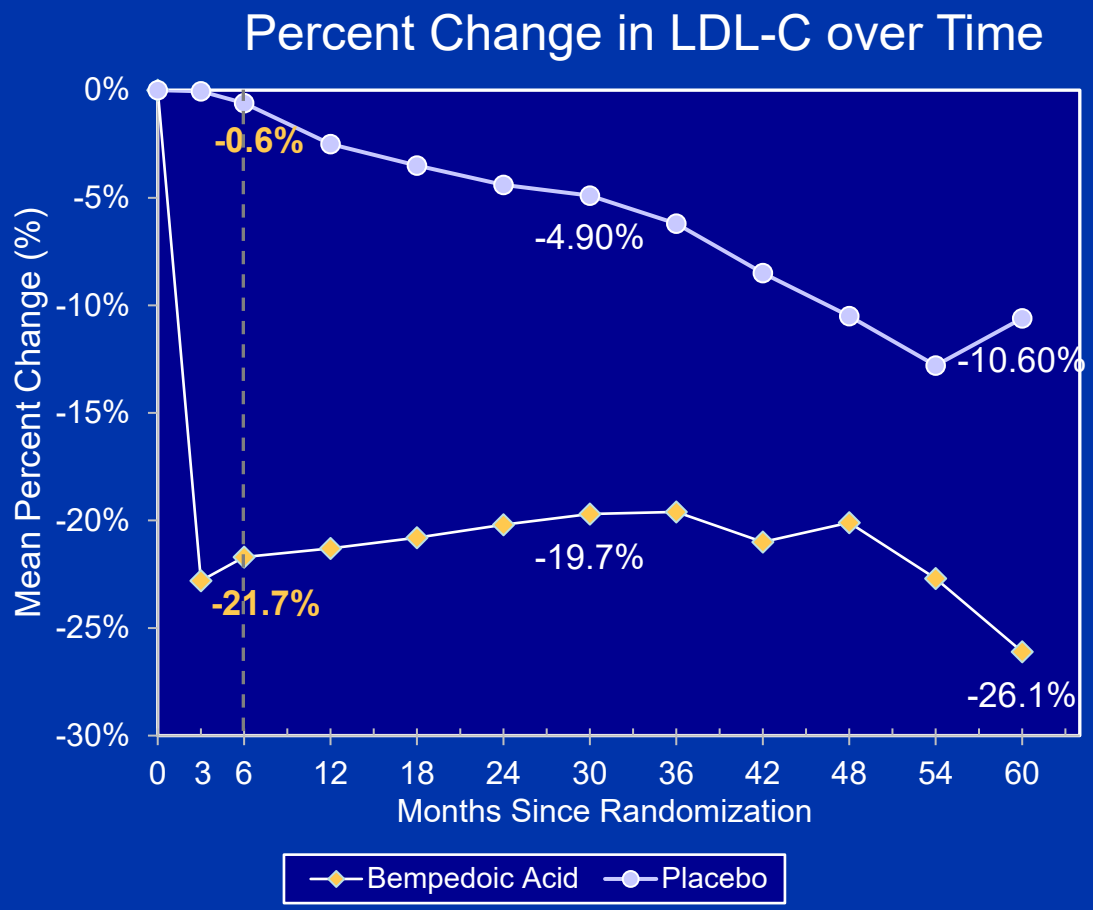
Study Milestones

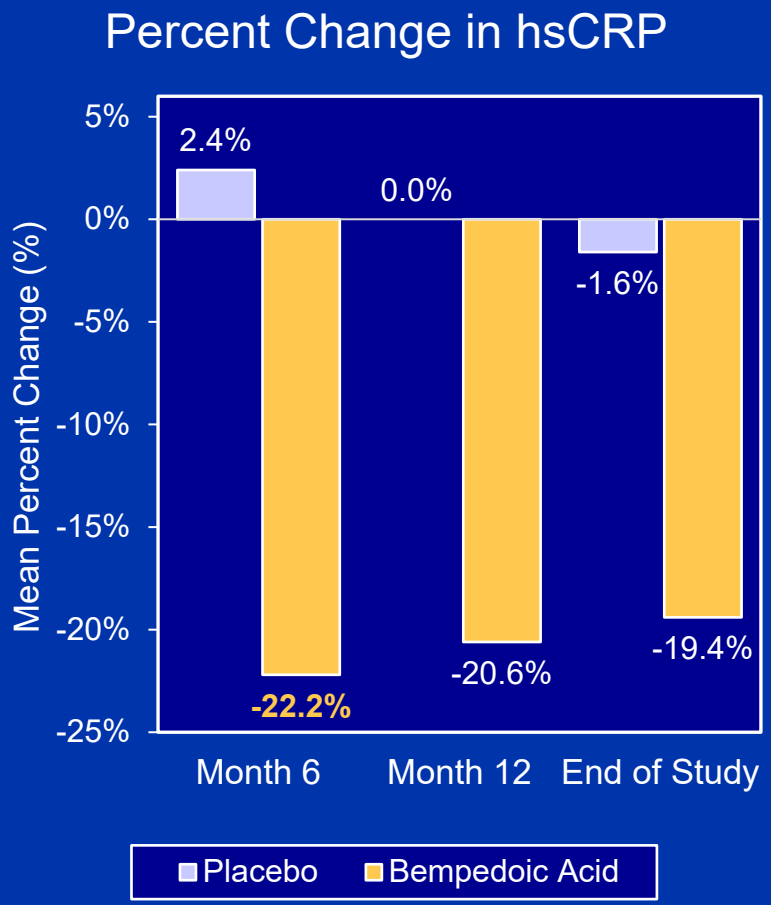
- 13,970 patients randomized at 1250 sites in 32 countries.
- Patients enrolled December 2016 to August 2019 with a median duration of follow-up 40.6 months.
- Despite the pandemic, complete assessment for the primary endpoint in 95.3% and vital status in 99.4% of patients.
- 4-component MACE occurred in 1746 patients and 3-component MACE in 1238 patients.

Selected Baseline Characteristics

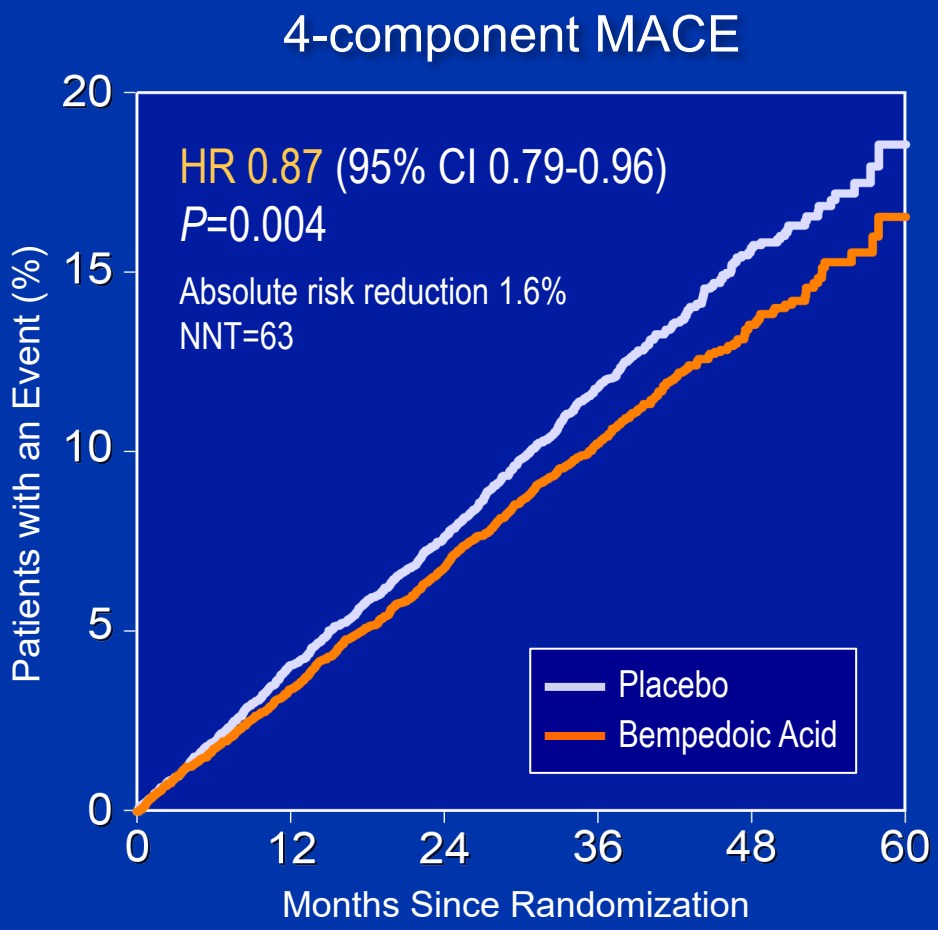
Characteristic	Bempedoic Acid N=6992	Placebo N=6978
Mean Age (years)	65.5	65.5
Female sex	48.1%	48.4%
White	91.5%	90.8%
LDL cholesterol (mg/dL)	139.0	139.0
HDL cholesterol (mg/dL)	49.6	49.4
hsCRP (mg/L)	2.3	2.3
High Risk Primary Prevention	30.0%	30.2%
Secondary Prevention	70.0%	69.8%
Diabetes	45.0%	46.3%
Baseline statin use	22.9%	22.5%

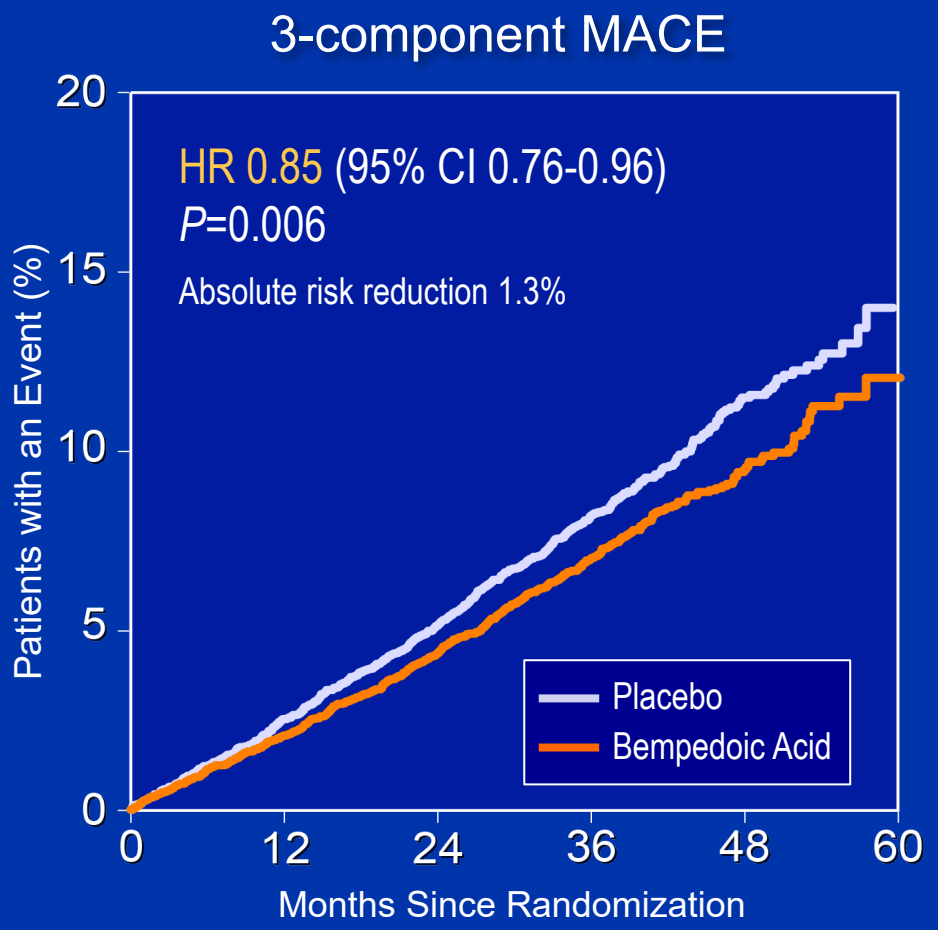
Effect of Trial Regimens on LDL-C and hsCRP



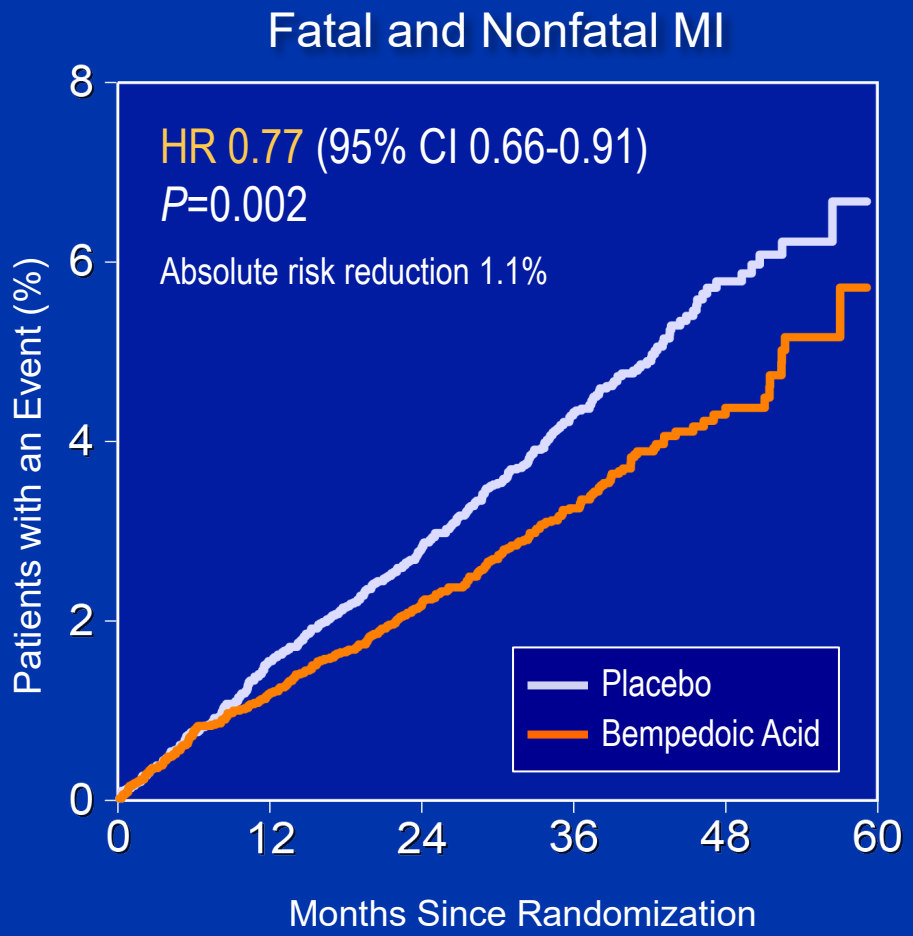


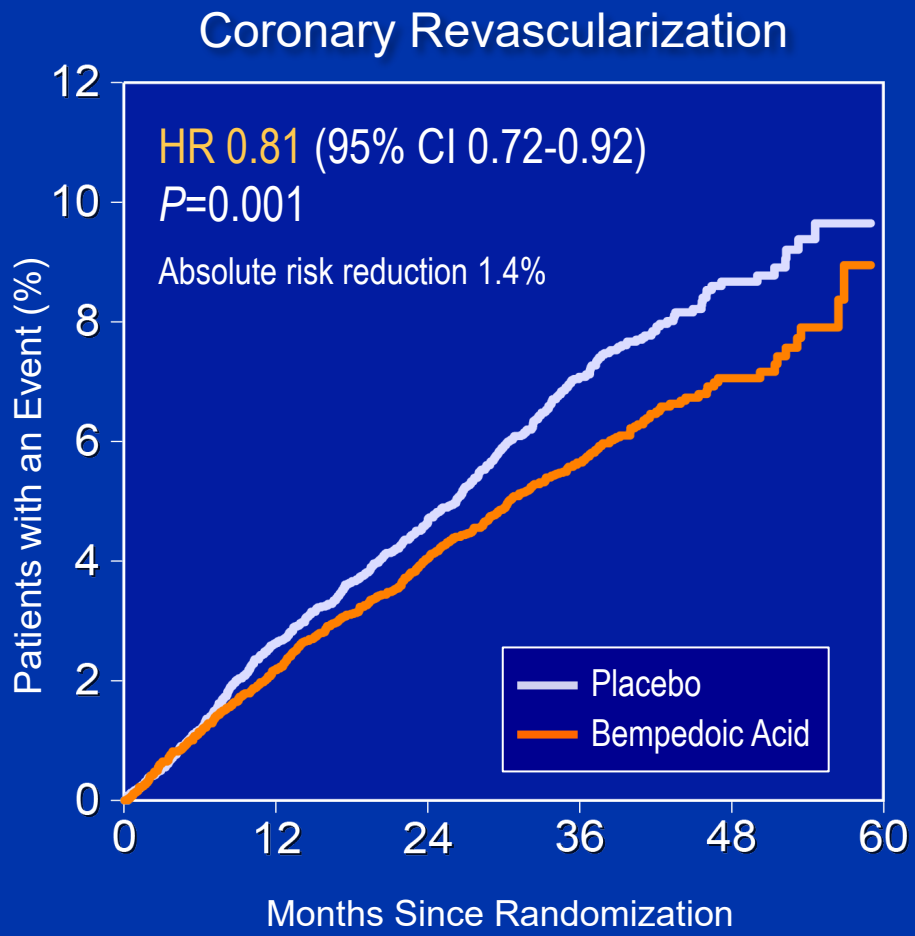
Primary and First Key Secondary Cardiovascular End Points



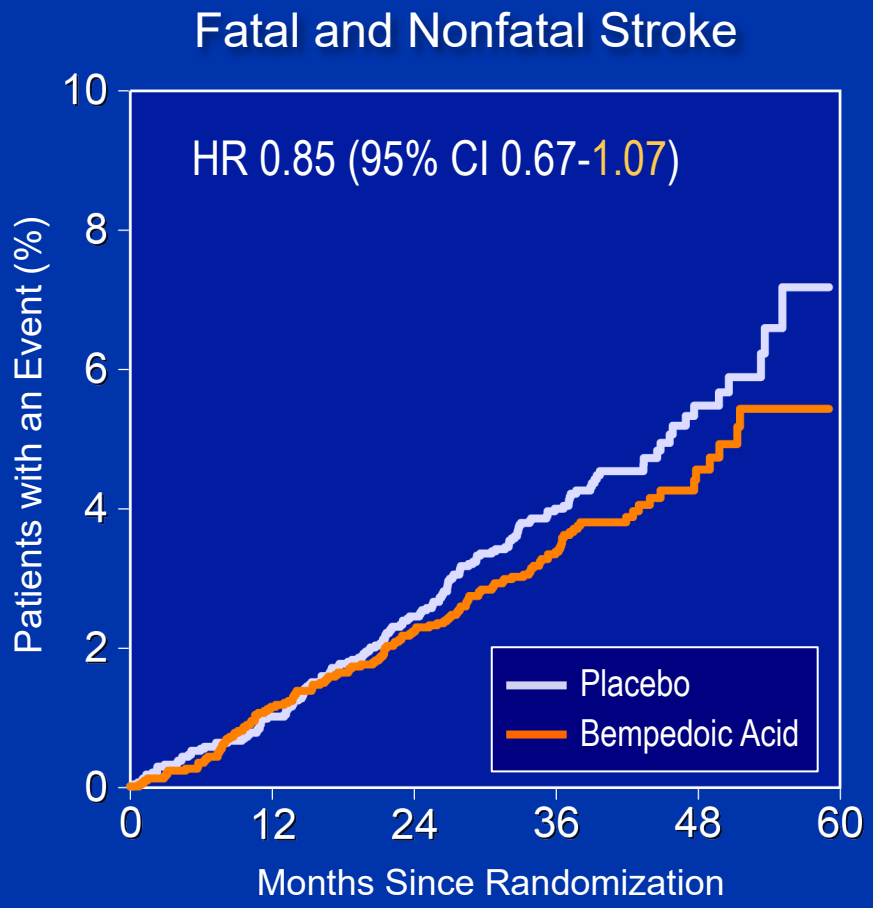


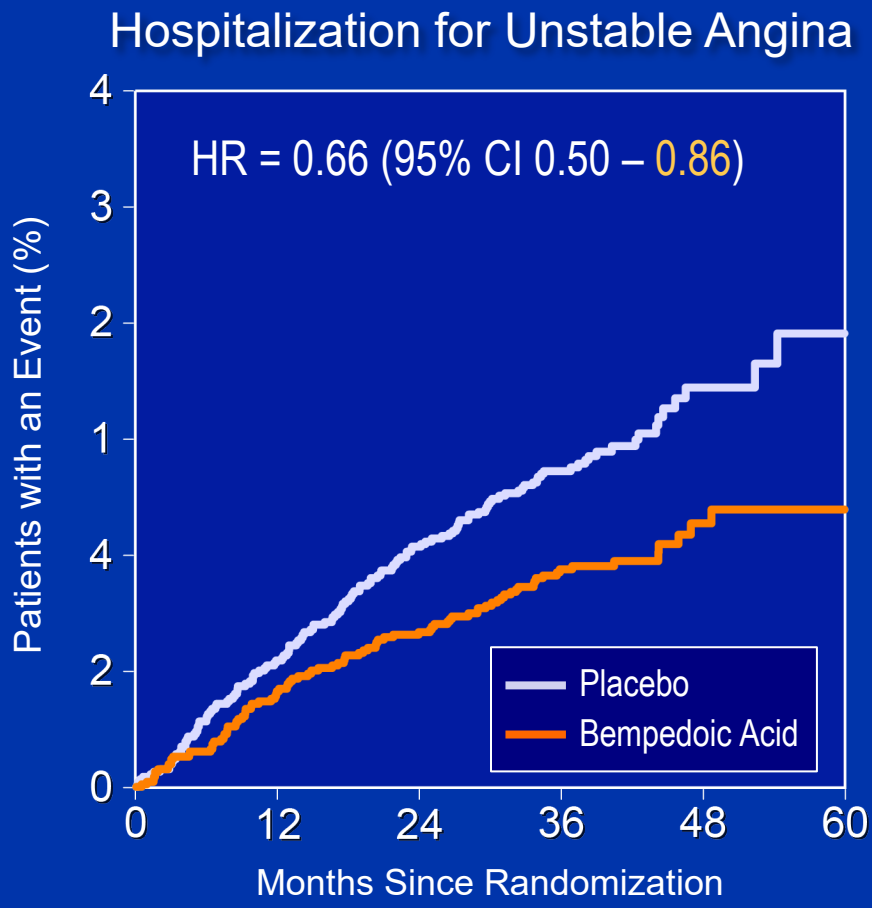
Key Secondary End Point: MI and Coronary Revascularization



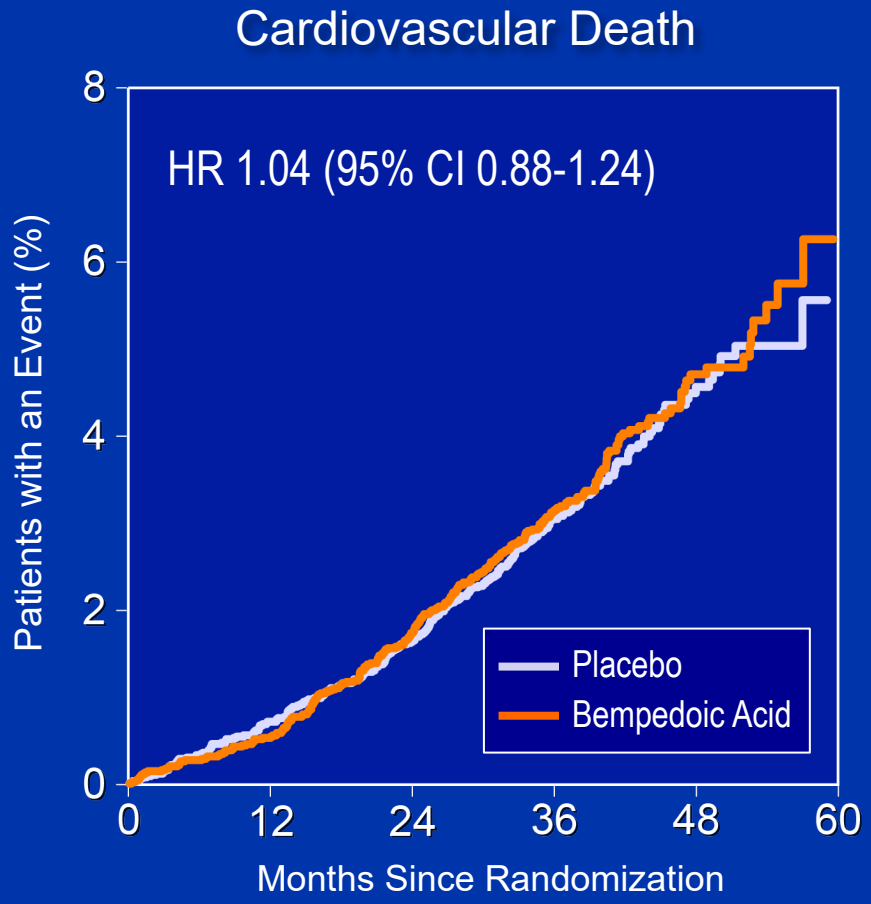


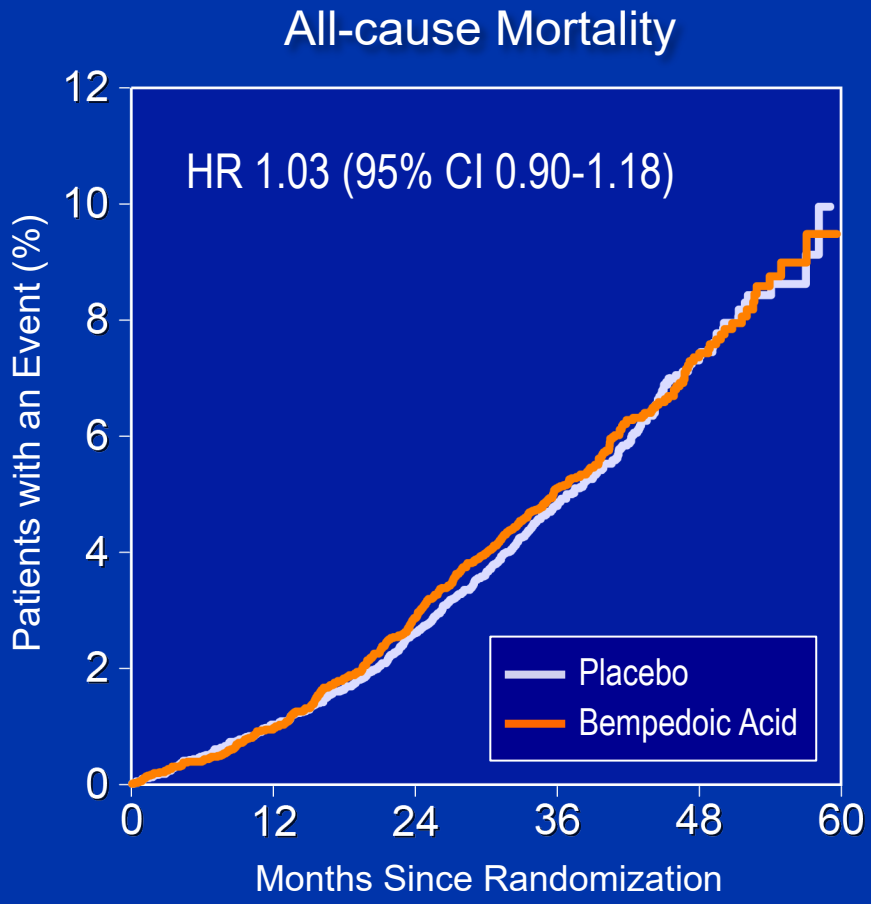
Effect on Stroke and Hospitalization for Unstable Angina





Effects of Trial Regimens on Mortality End Points

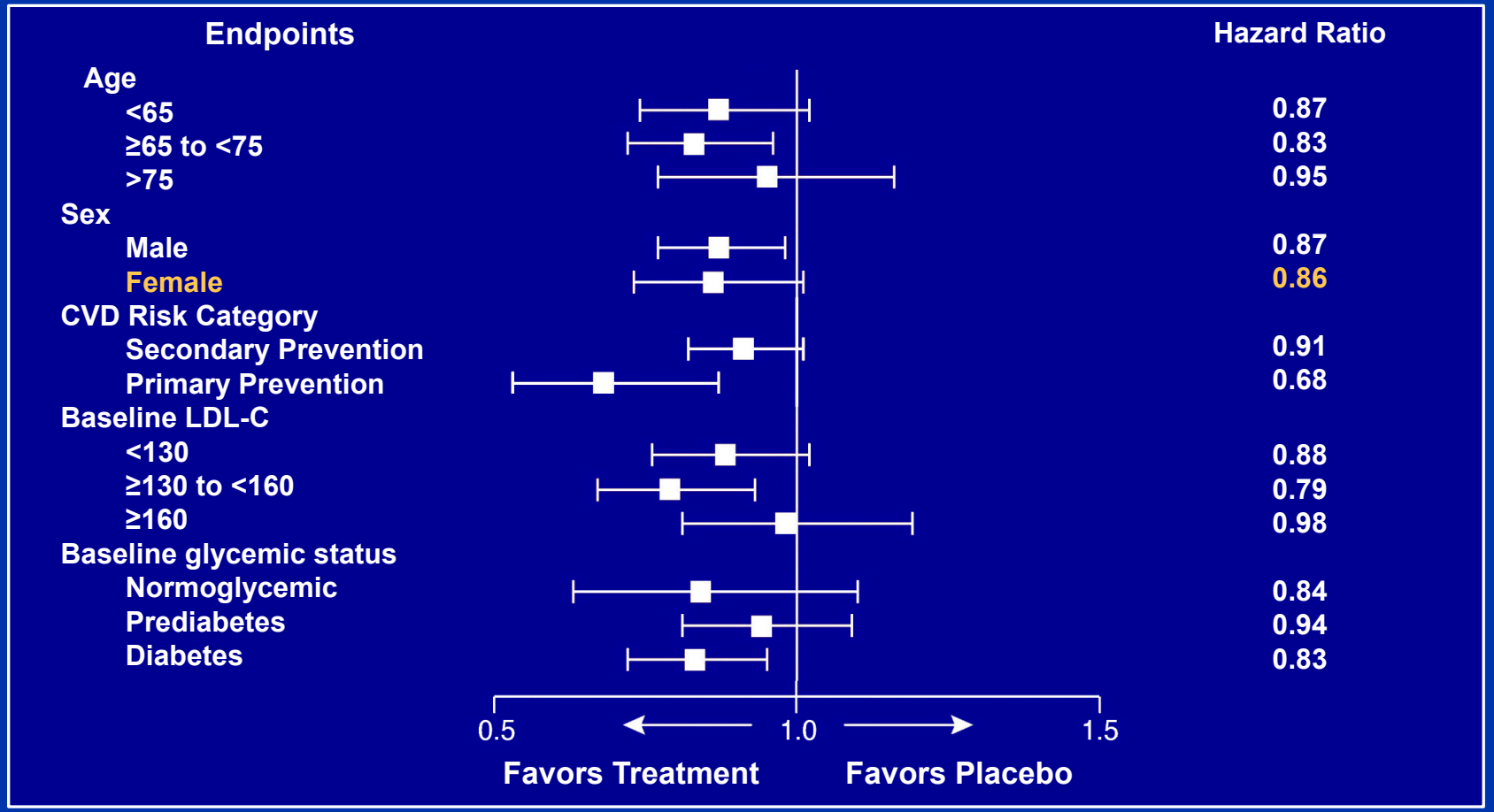




Investigator-Reported Adverse Effects

Characteristic	Bempedoic Acid N=7001	Placebo N=6964
Serious Treatment Emergent Adverse event	25.2%	24.9%
Adverse event leading to drug discontinuation	10.8%	10.4%
Any muscle disorder	15.0%	15.4%
New onset diabetes	16.1%	17.1%
Elevated hepatic enzymes	4.5%	3.0%
Prespecified renal events	11.5%	8.6%
Gout	3.1%	2.1%
Cholelithiasis	2.2%	1.2%
Adjudicated tendon rupture	1.2%	0.9%

Primary MACE-4 End Point in Selected Subgroups



Limitations

- The trial enrolled only patients with documented statin intolerance. Effects in other populations were not studied.
- Addition of other therapies (including PCSK9 inhibitors) narrowed the LDL-C differences between bempedoic acid and placebo over time.
- The pandemic created challenges in achieving complete follow up, although full outcome data were available in 95.3% of patients and vital status determined in 99.4%.

Conclusions

- Bempedoic acid was well-tolerated in a mixed population of primary and secondary prevention patients unable or unwilling to take statins
- Bempedoic acid lowered LDL-C by 21.7% and hsCRP by 22.2% with small increases in the incidence of gout and cholelithiasis.
- The primary end point, 4-component MACE was reduced 13%, 3-component MACE 15%, myocardial infarction 23% and coronary revascularization 19%.
- These findings establish bempedoic acid as an effective approach to reduce major cardiovascular events in statin intolerant patients.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D.E. Grobbee, M.J. Louie, C.-F. Chen, N. Li, L.A. Bloedon, P. Robinson, M. Horner, W.J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, and S.J. Nicholls, for the CLEAR Outcomes Investigators*

ABSTRACT

BACKGROUND

Bempedoic acid, an ATP citrate lyase inhibitor, reduces low-density lipoprotein (LDL) cholesterol levels and is associated with a low incidence of muscle-related adverse events; its effects on cardiovascular outcomes remain uncertain.

A Final Thought

Management of patients unable or unwilling to take statins represents a challenging and frustrating clinical issue.

Regardless whether this problem represents the nocebo effect or actual intolerance, these high-risk patients need effective alternative therapies.

The CLEAR Outcomes trial provides a sound rationale for use of bempedoic acid to reduce major adverse cardiovascular outcomes in patients intolerant to statins.

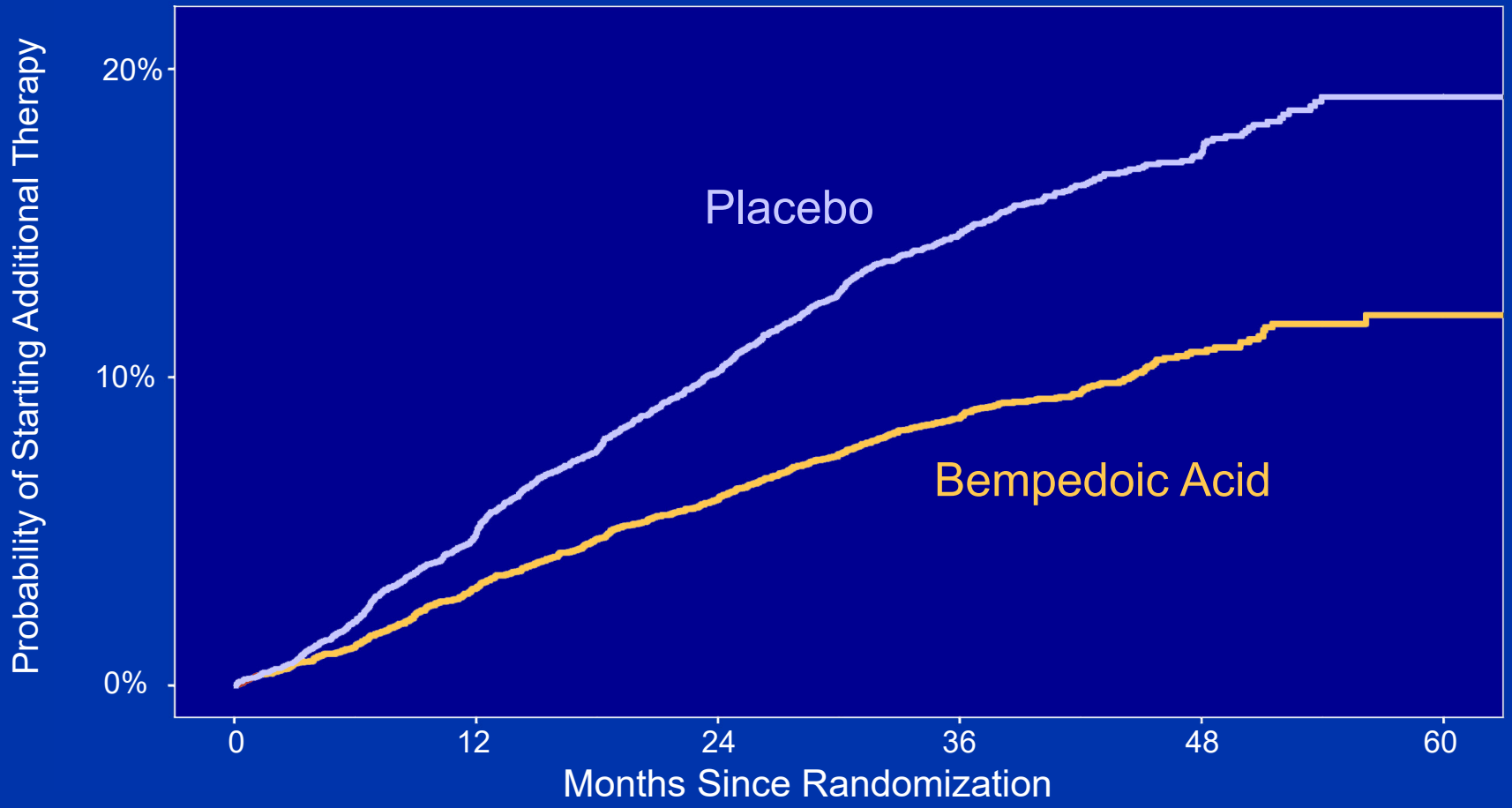
Backup

Summary of All LMT Cross-ins During the Trial

LMT Category	Bempedoic Acid (N = 6992)	Placebo (N = 6978)
Any LMT	660 (9.4%)	1089 (15.6%)
Statins*	283 (4.0%)	456 (6.5%)
PCSK9 inhibitors -mAb	194 (2.8%)	306 (4.4%)
Selective Cholesterol Absorption Inhibitors (Ezetimibe)	189 (2.7%)	382 (5.5%)
Fibrates	72 (1.0%)	91 (1.3%)
Bile Acid Sequestrants	11 (0.2%)	17 (0.2%)
Bempedoic Acid	11 (0.2%)	10 (0.1%)
Fixed Dose Combination: Bempedoic Acid + Ezetimibe	6 (0.1%)	3 (<0.1%)
PCSK9-siRNA	4 (0.1%)	5 (0.1%)
Niacin derivatives	4 (0.1%)	6 (0.1%)

* At the end of the study <4% patients receiving a moderate or high intensity statin

Time to Cross-in to Additional Lipid Modifying Therapy



CTTC End Point Calculation

Bempedoic Acid (N=6992), n (%)	Placebo (N=6978), n (%)	HR	P-value
703 (10.1)	816 (11.7)	**0.85 (0.77,0.94)**	0.001

	Bempedoic Acid (N=6992)	**Placebo (N=6978)**
Baseline, n	6992	6978
Mean (SD)	139.0 (34.9)	139.0 (35.2)
Month 12, n	5977	5824
Mean (SD)	107.2 (37.8)	133.2 (41.4)
Change from baseline, LS Mean (SE)	-28.5 (0.42)	-2.47 (0.43)
Difference of LS Means (SE)	-26.1 (0.59) mg/dl **(0.67 mmol/L)**	

CTTC calculation = Expected HR for 0.67 mmol/L LDL-C reduction = **0.846**

Outcomes: Non-Statin LDL-C Lowering Therapies

	3-Component MACE	Nonfatal MI
Ezetimibe	0.90	0.87
Evolocumab	0.80	0.73†
Alirocumab	0.86*	0.86
Bempedoic Acid	0.85	0.73

*Trial used all-cause mortality rather than CV death

†Fatal and nonfatal MI