#AHA24

BEMPEDOIC ACID AND LIMB OUTCOMES IN STATIN-INTOLERANT PATIENTS WITH PERIPHERAL ARTERY DISEASE: NEW INSIGHTS FROM THE CLEAR OUTCOMES TRIAL

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American Heart Association.

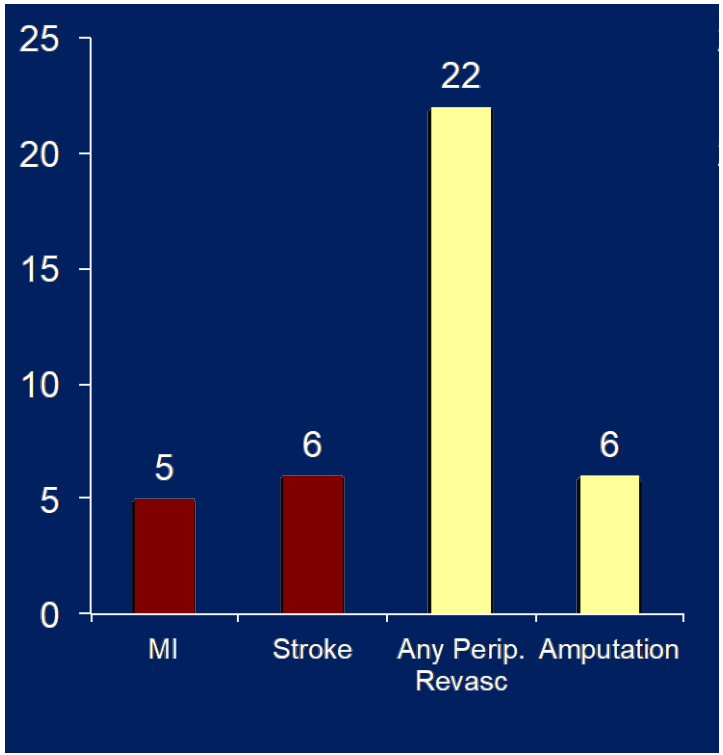
American Heart Association. 100 YEARS Bold Hearts

DISCLOSURES

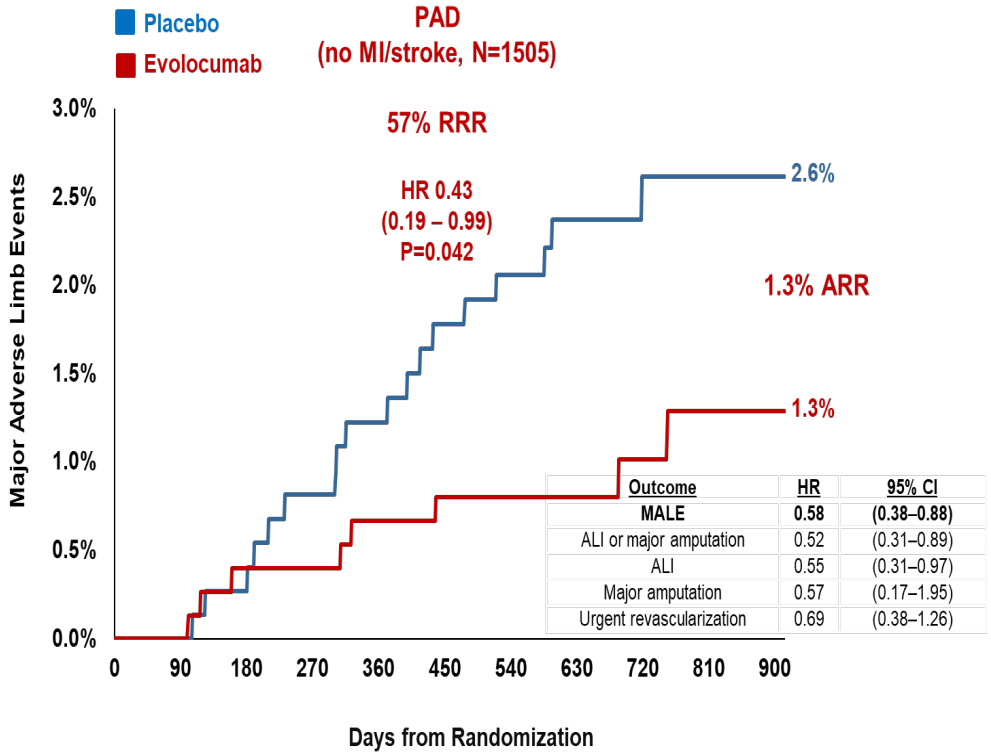
Dr. Bonaca is the Executive Director of CPC, a non-profit academic research organization affiliated with the University of Colorado, that receives or has received research grant/consulting funding from: Abbott Laboratories, Alnylam Pharmaceuticals, Inc., Amgen Inc., Angionetics, Inc., Anthos Therapeutics, Array BioPharma, Inc., AstraZeneca and Affiliates, Atentiv LLC, Bayer and Affiliates, Bristol-Meyers Squibb Company, CellResearch Corp., Cleerly Inc., CSL Behring LLC, Eidos Therapeutics, Inc., Esperion Therapeutics, Inc., Faraday Pharmaceuticals, Inc., HDL Therapeutics Inc., HeartFlow Inc., Hummingbird Bioscience, Insmed Inc., Ionis Pharmaceuticals, Johnson and Johnson Affiliates, Lexicon Pharmaceuticals, Inc., Merck & Affiliates, Nectero Medical Inc., Novartis Pharmaceuticals Corp., Novo Nordisk, Inc., Osiris Therapeutics Inc., Pfizer Inc., PhaseBio Pharmaceuticals, Inc., Prothena Biosciences Limited, Regeneron Pharmaceuticals, Inc., Regio Biosciences, Inc., Sanofi-Aventis Groupe, Silence Therapeutics PLC, Silence, Stealth BioTherapeutics Inc., Structure Therapeutics

BACKGROUND – MAJOR ADVERSE LIMB EVENTS

Events in PAD Patients at 4 Years REACH Registry



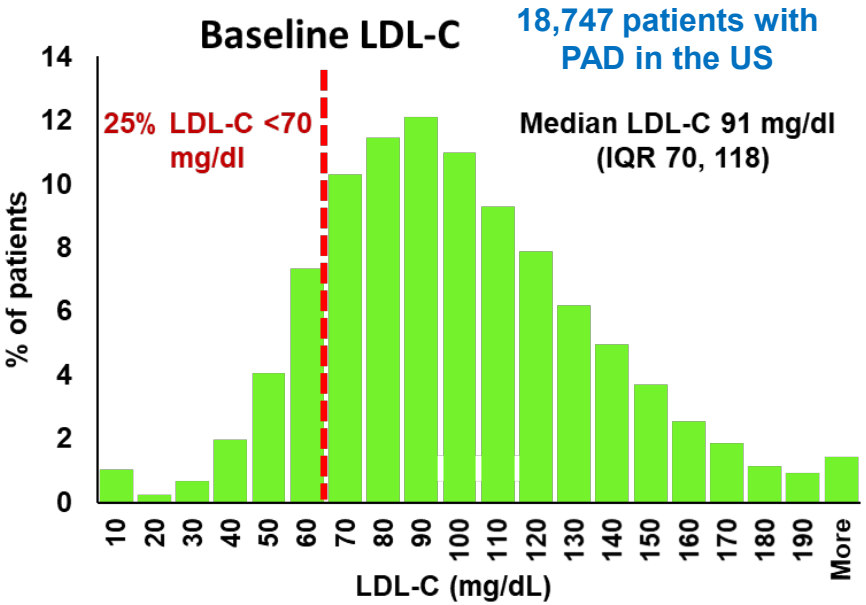
Limb Outcomes with PCSK9 Inhibition in FOURIER

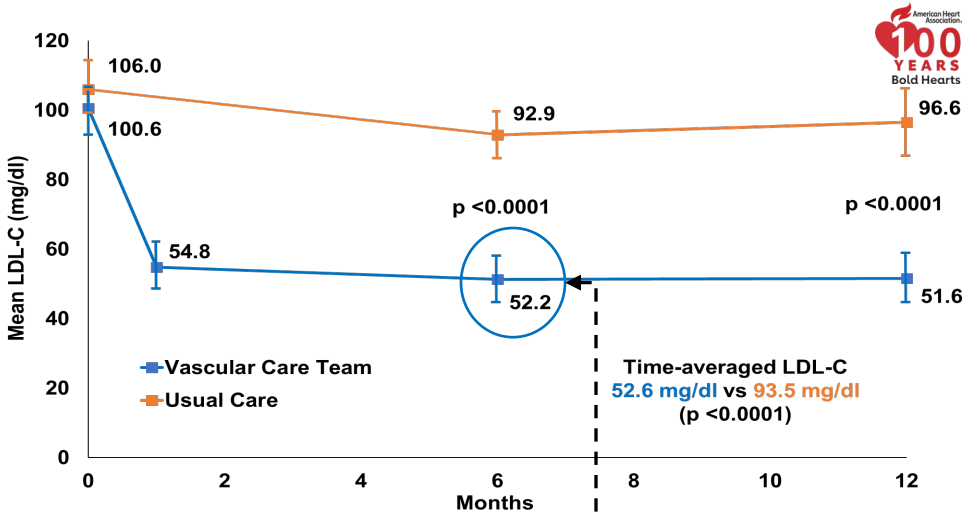


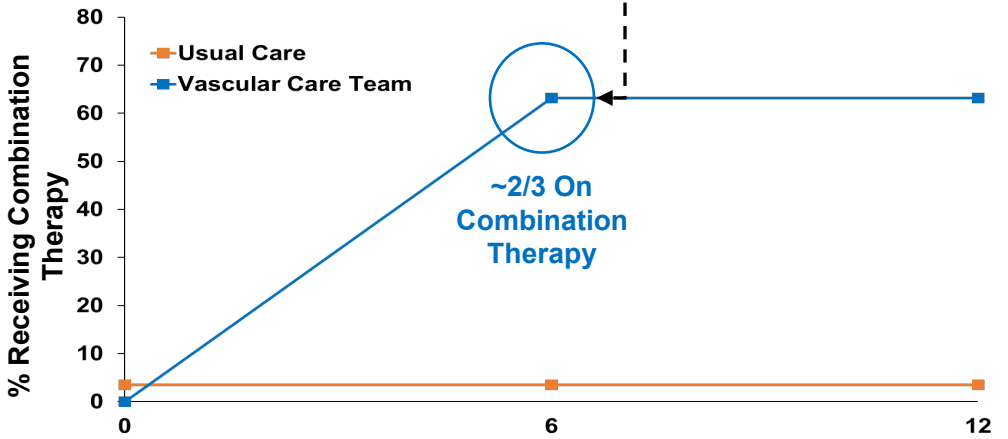
Kumbhani et al. EHJ 2014; Bonaca et al. Circulation 2018

BACKGROUND

- Most patients with PAD fail to achieve an LDL-C < 70 mg/dL (let alone <55 mg/dL…)
- Combination therapy may be needed in ~2/3 to achieve LDL-C Targets



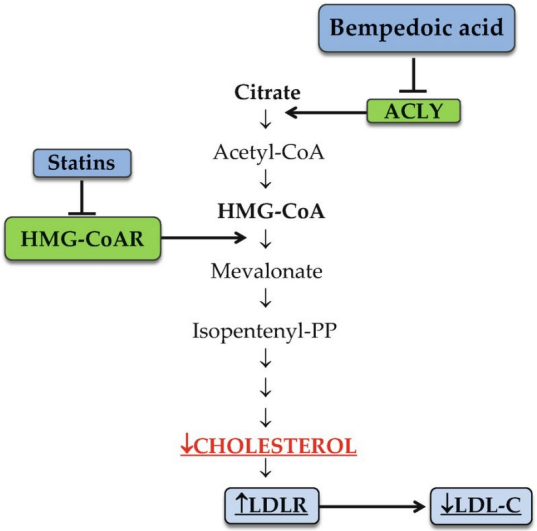




BACKGROUND

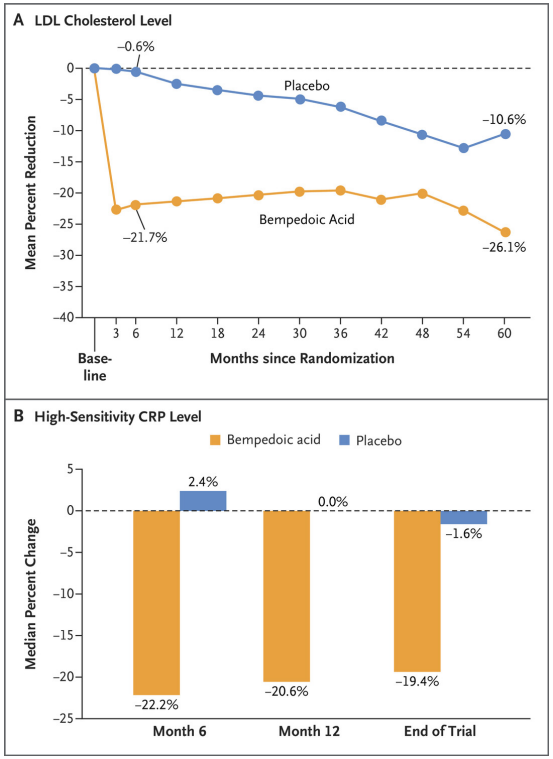
Bempedoic acid:

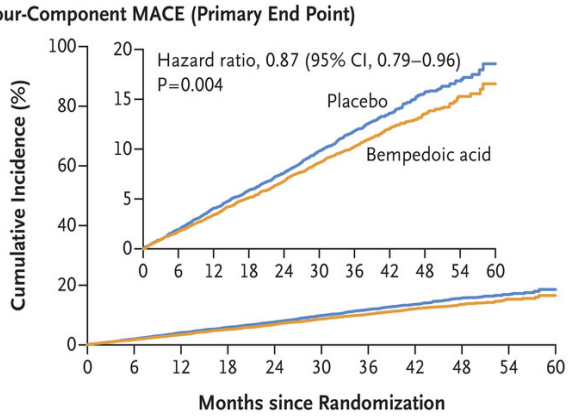
- **ATP citrate lyase (ACLY) inhibitor**
- **acts upstream of statins**



- **Oral – alone or in combination with ezetimibe and/or statins**
- **Well tolerated & does not increase HbA1C or incidence of new onset T2DM**

Lowers low-density lipoprotein (LDL) cholesterol levels, lowers hsCRP





No. at Risk

Placebo	6978	6779	6579	6401	6206	5995	5105	2524	1207	513	55
Bempedoic acid	6992	6816	6654	6472	6293	6106	5257	2601	1240	556	74

Event	Bempedoic Acid	Placebo
Serious Adverse Event	25.2%	24.9%
Hepatic	4.5%	3.0%
Renal	11.5%	8.6%
Myalgia	5.6%	6.8%
Gout	3.1%	2.1%

Pirillo A, Norata GD, Catapano AL. LDL-Cholesterol-Lowering Therapy. 2020 Apr 30. In: von Eckardstein A, Binder CJ, editors. Prevention and Treatment of Atherosclerosis: Improving State-of-the-Art Management and Search for Novel Targets [Internet]. Cham (CH): Springer; 2022. Fig. 4; Nissen SE et al. NEJM 2023

TRIAL COHORT

Patients 18 to 85 years of age at increased cardiovascular risk

- **A previous cardiovascular event (secondary-prevention patients)**
- **Clinical features that placed them at high risk for a cardiovascular event (primary-prevention patients)**

Eligible patients had to report being unable or unwilling to receive statins owing to an adverse effect that had started or increased during statin therapy and resolved or improved after statin therapy was discontinued ("statin-intolerant" patients). Other lipid-lowering therapies were permitted, such as ezetimibe, niacin, bile acid resins, fibrates, or proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors, administered as monotherapy or in combinations

Symptomatic peripheral arterial disease (PAD), defined by:

- **Peripheral vascular disease with symptoms of claudication or resting limb ischemia with either ankle brachial index <0.9 or angiogram (including CTA) showing ≥50% stenosis (ankle brachial index will be measured after a period of rest and with the patient in the supine position using a Doppler device), or**
- **Peripheral arterial revascularization (surgical or percutaneous), occurring greater than 90 days prior to screening, or**
- **Lower extremity amputation due to peripheral vascular disease, occurring greater than 90 days prior to screening**

AIMS & METHODS

Aims

- To describe the risk of major adverse limb events (MALE) in patients with peripheral artery disease
- To evaluate the effect of bempedoic acid on MALE & MACE+MALE for first and total events

Methods

Current Analysis Primary Endpoint of MALE defined as composite of all

- Worsening PAD – worsening symptoms leading to spontaneous reporting of an adverse event and leading to revascularization
- Chronic limb threatening ischemia (CLTI)
- Acute limb ischemia (ALI)

Two blinded (treatment, LDL), trained, vascular medicine specialists independently reviewed all reported SAEs and categorized by pre-specified definitions

Trial Primary end point – MACE 4 = CV death, MI, stroke, or coronary revascularization;

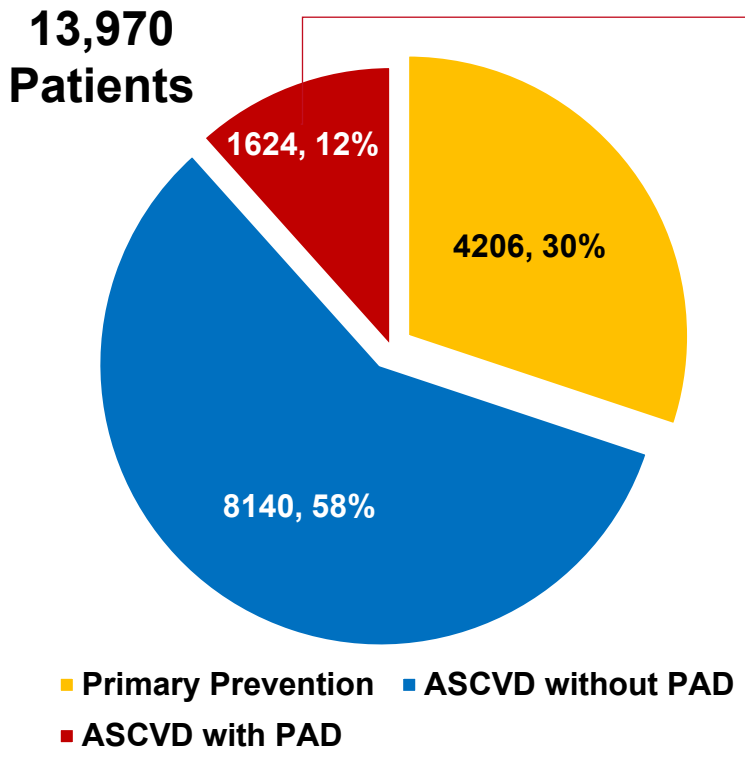
Key Secondary end point - MACE 3 = CV death, MI, stroke

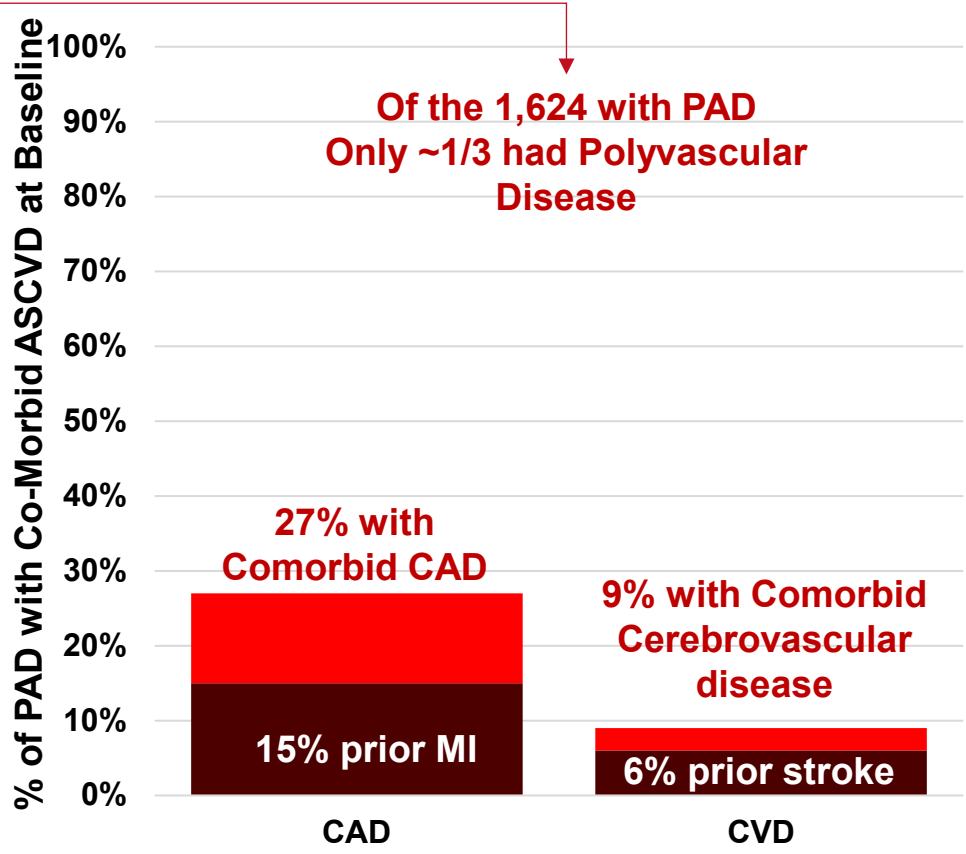
Primary analysis was time to first event as intention to treat (ITT); Total events were analyzed by a negative binomial model to get the RR estimates. All reported analyses were adjusted for selected baseline factors. Post-hoc results are descriptive in nature instead of confirmatory. Multiplicity is not adjusted/corrected.

RESULTS – BASELINE CHARACTERISTICS

Characteristics	Patients with PAD N=1,624	Patients with no PAD N=12,346
Age, mean (SD), years	63.9 (9.9)	65.7 (8.8)
Female sex, %	56%	47%
White, %	89%	91%
Hispanic or Latinx, %	28%	15%
BMI, mean (SD), kg/m^2	29.6 (5.4)	30.0 (5.2)
LDL Cholesterol		
Mean (SD), mg/dl	138.9 (33.5)	139.0 (35.2)
Distribution		
<130 mg/dl	714 (44.0%)	5449 (44.1%)
≥130 to <160 mg/dl	512 (31.5%)	3951 (32.0%)
≥ 160 mg/dl	398 (24.5%)	2946 (23.9%)
HDL Cholesterol Mean (SD), mg/dl	50.0 (13.2)	49.5 (13.3)
Non-HDL Cholesterol Mean (SD), mg/dl	174.6 (38.3)	173.8 (40.0)
Total Cholesterol Mean (SD), mg/dl	224.6 (39.1)	223.2 (41.1)
Triglycerides, Median (IQR), mg/dl	163.0 (119.5 - 223.5)	158.5 (117.5 - 214.5)
High-sensitivity CRP, Median (IQR), mg/dl	2.6 (1.4 - 5.3)	2.3 (1.1 - 4.4)
Estimated GFR <60 ml/min/1.73^2, %	20%	21%
Statin %	21%	23%
Ezetimibe %	12%	12%
PCSK9i %	0.7%	0.6%

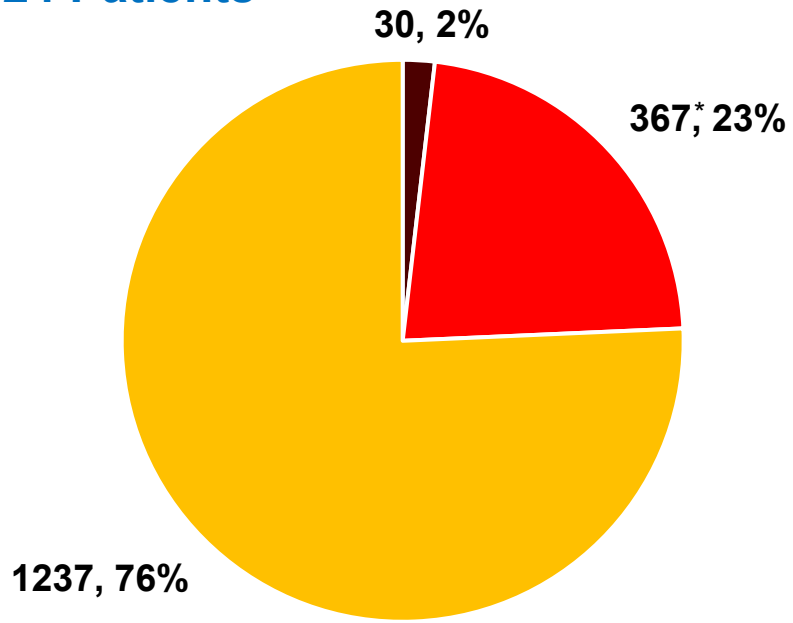
RESULTS – DISTRIBUTION OF ASCVD





RESULTS – PAD HISTORY & EVENT DISTRIBUTION

1,624 Patients

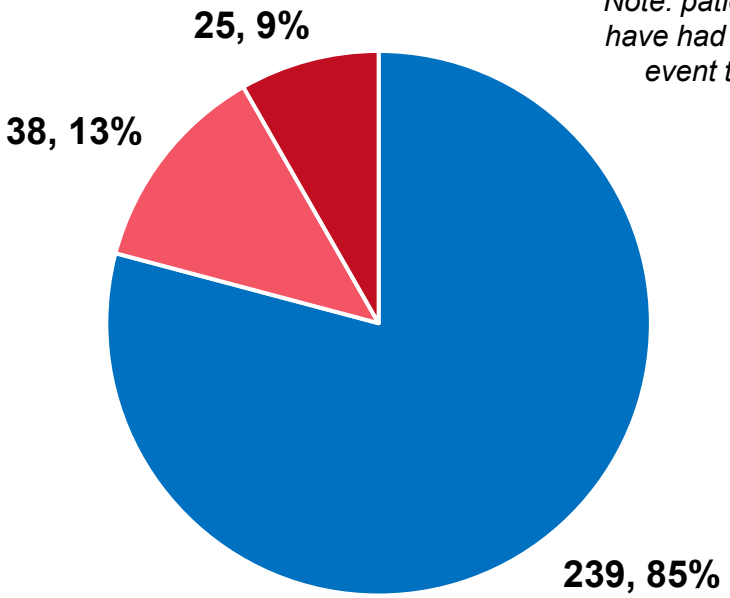


- Prior Amputation
- Prior Revascularization
- Chronic PAD without Amputation or Revascularization

*10 patients had a history of both amputation and revascularization

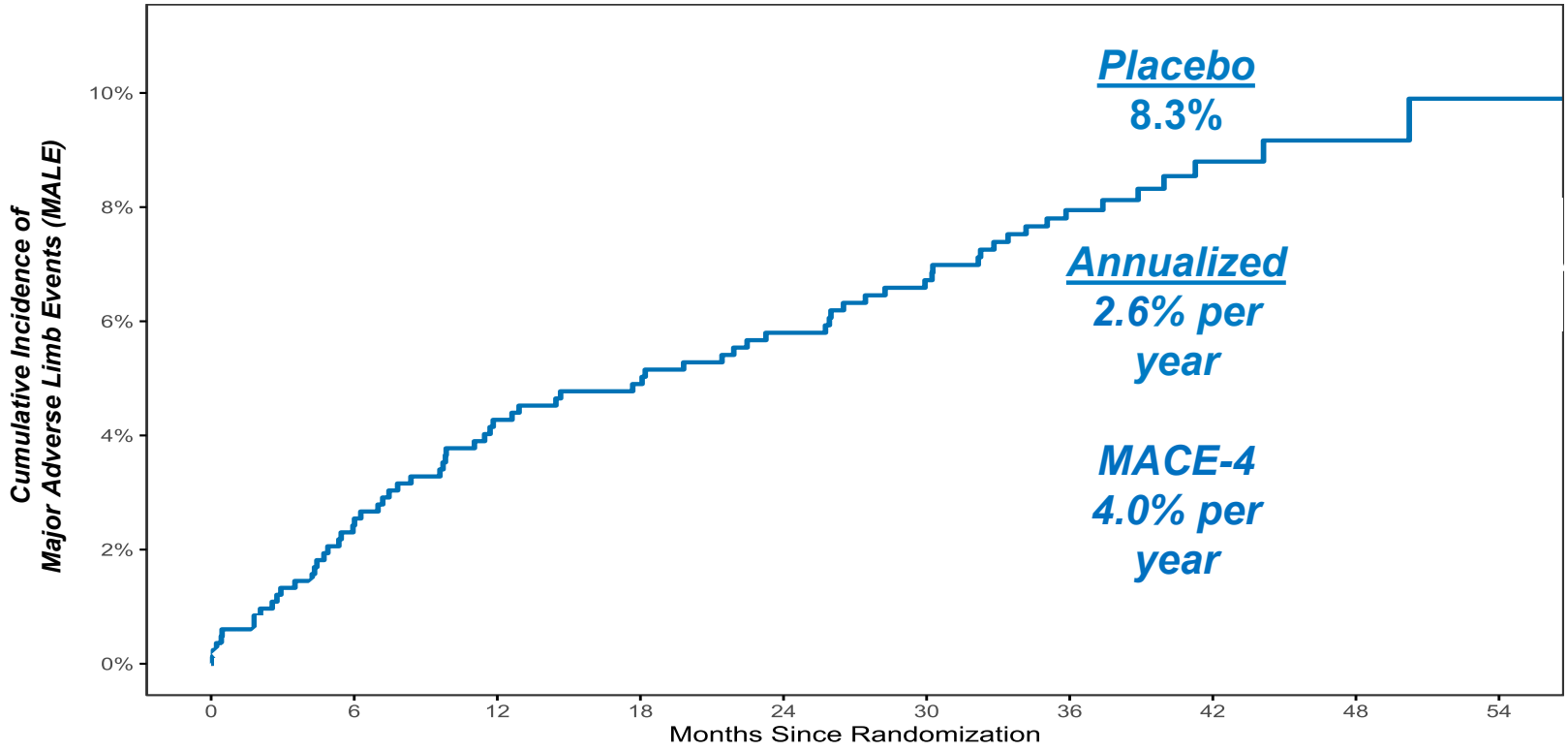
282 Patients with Events (115 in PAD, 167 in no PAD)

*Note: patients may have had multiple event types



- Worsening PAD --> Revasc
- CLTI
- ALI

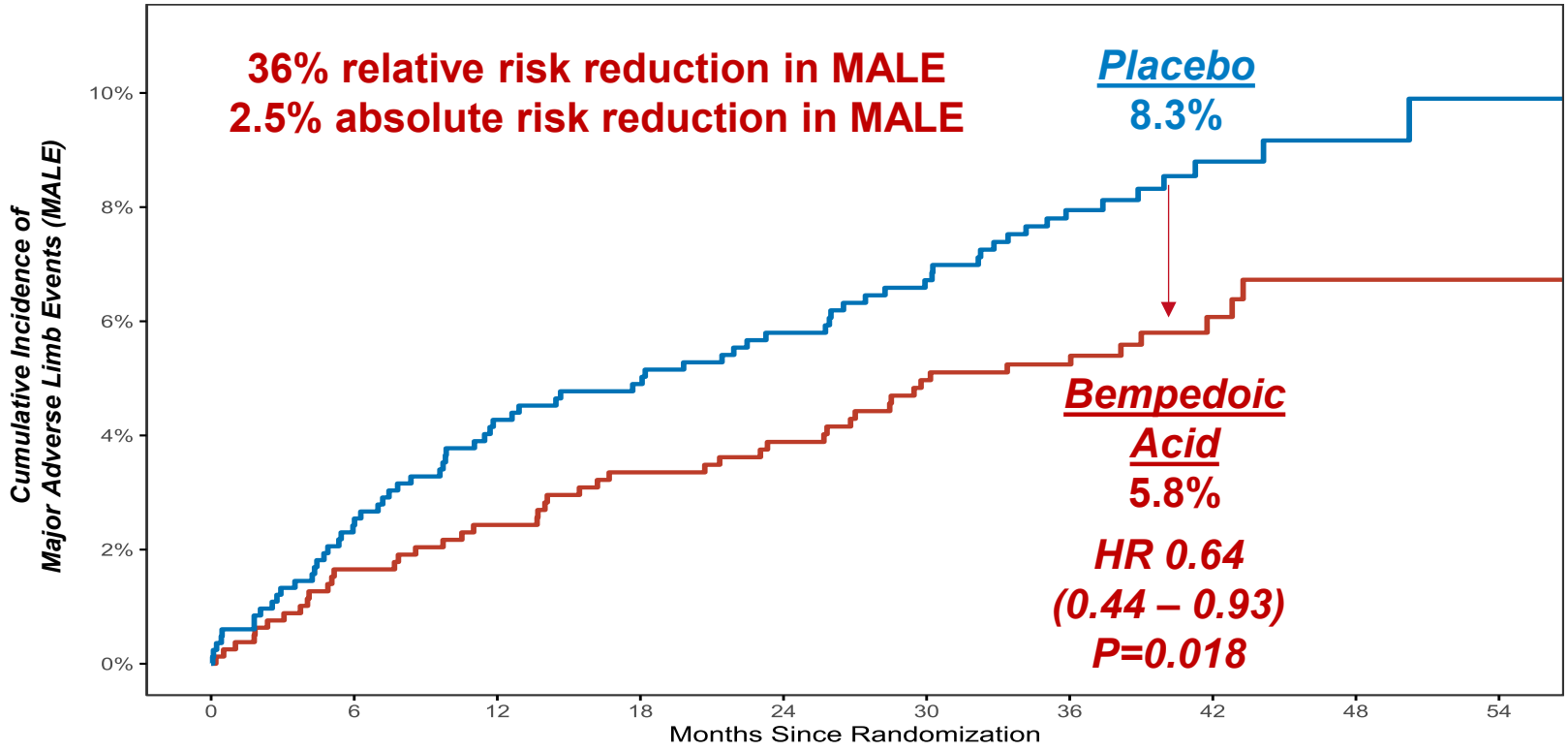
RESULTS – RISK OF MALE IN PATIENTS WITH PAD



No. at Risk										
Bempedoic Acid	794	768	747	731	717	699	624	334	159	71
Placebo	830	802	767	751	723	702	624	331	160	77

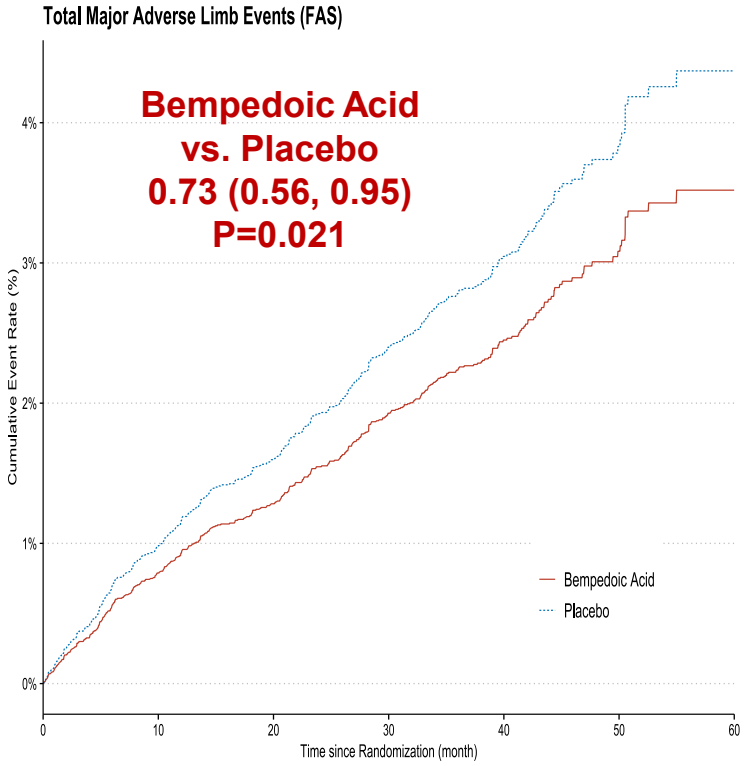
First events, ITT

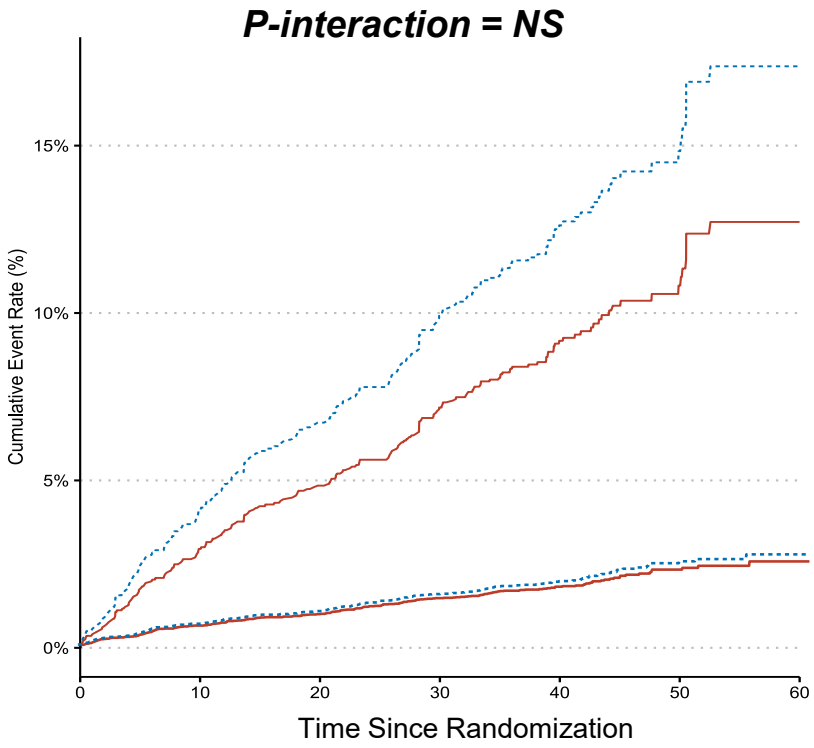
RESULTS – RISK OF MALE IN PATIENTS WITH PAD



First events, ITT

RESULTS – BEMPEDOIC ACID AND TOTAL MALE



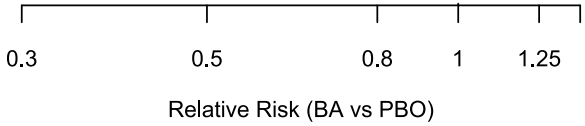


1,624 with PAD
HR 0.55
(0.35, 0.85)
P=0.007

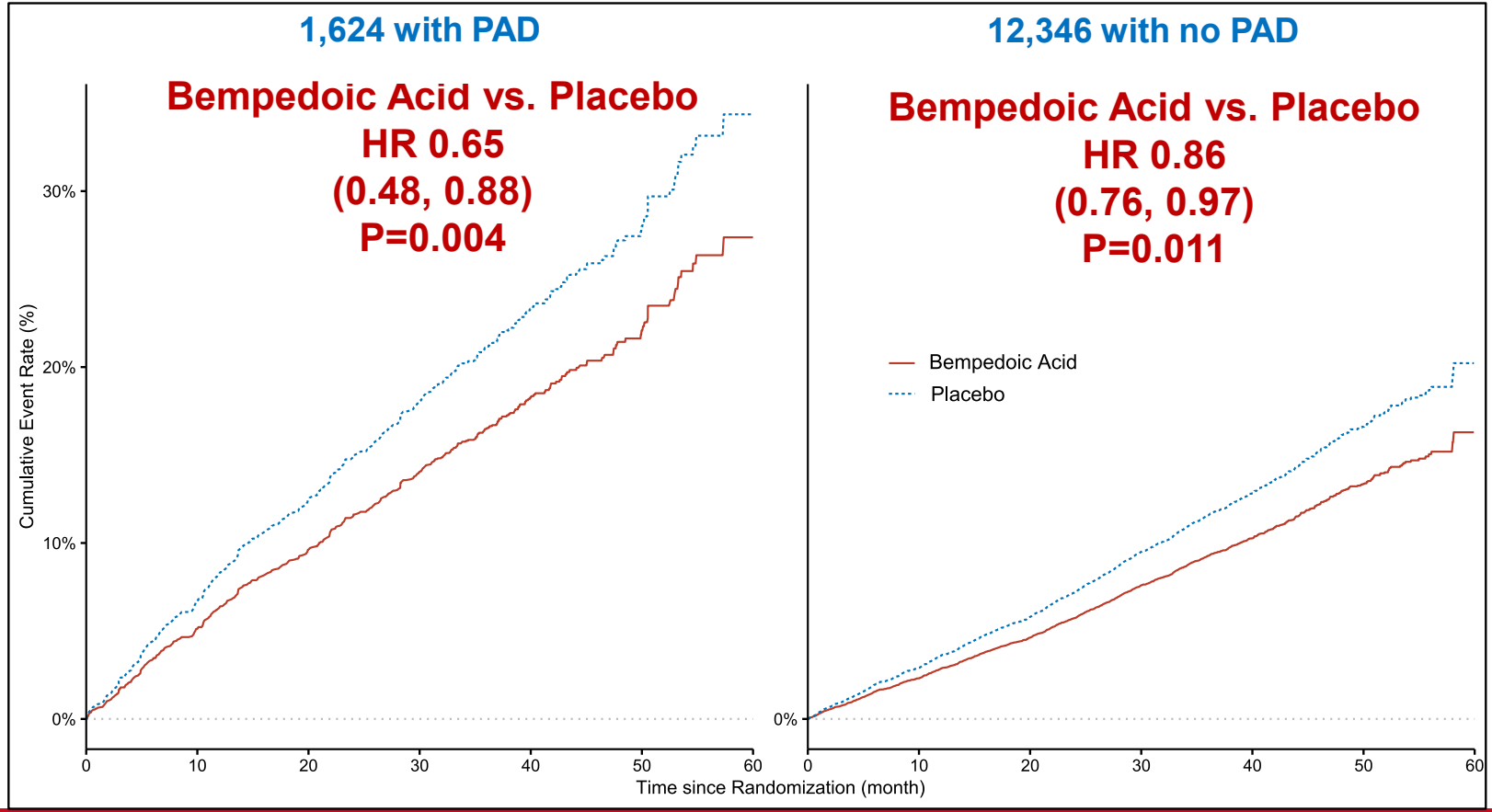
12,346 with no PAD
HR 0.90
(0.64, 1.26)
P=0.53

RESULTS – BEMPEDOIC ACID WITH & WITHOUT PAD

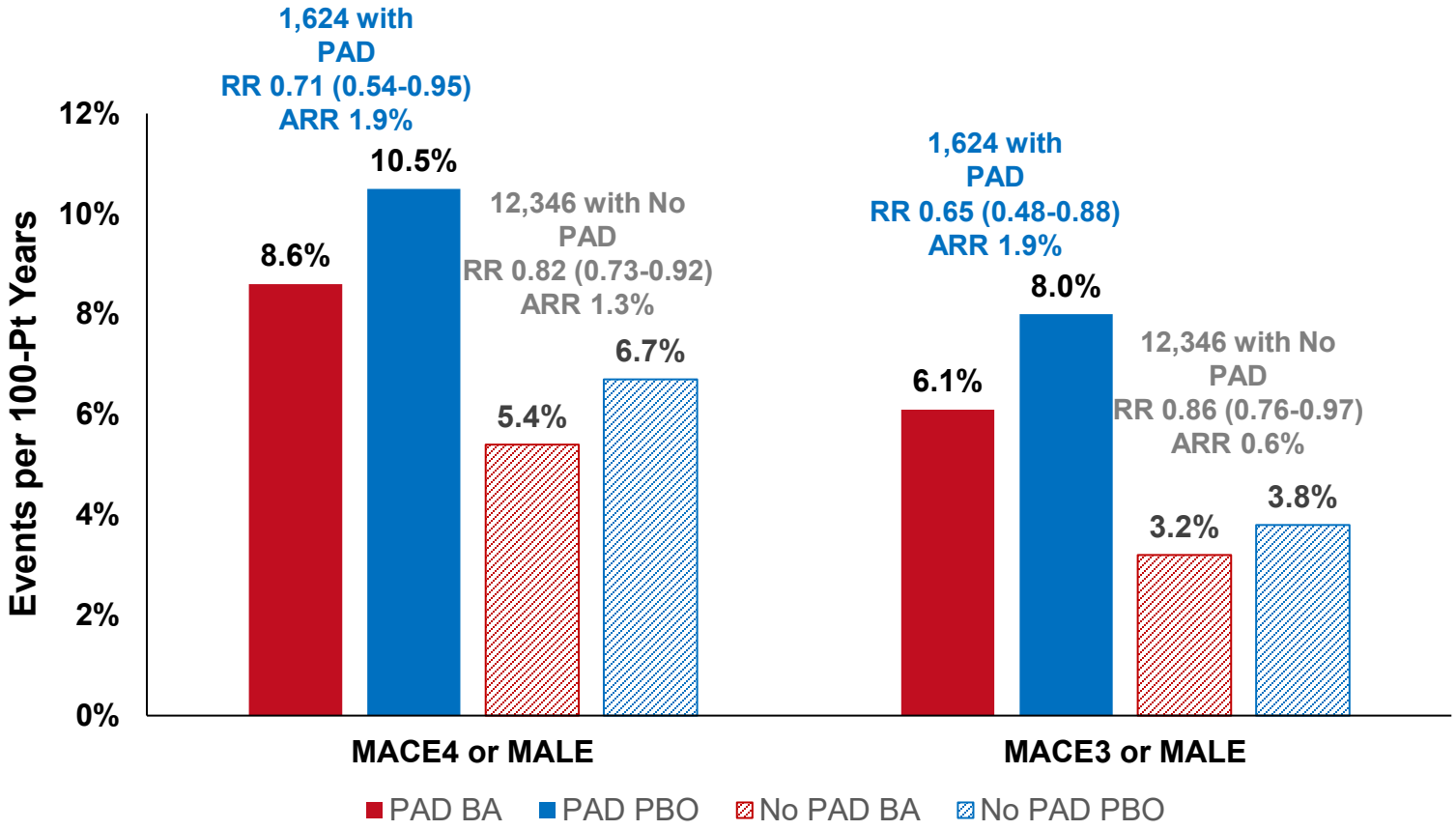
Parameter Overall PAD History	Bempedoic Acid n (/100py)	Placebo n (/100py)	Relative Risk [95% CI]
Primary Endpoint MACE-4	1190 (5.0)	1471 (6.2)	0.82 [0.73, 0.92]
PAD	156 (5.7)	184 (6.5)	0.83 [0.59, 1.16]
No PAD	1034 (4.9)	1287 (6.2)	0.82 [0.73, 0.92]
MACE-3	660 (2.8)	793 (3.4)	0.83 [0.74, 0.94]
PAD	88 (3.2)	114 (4.0)	0.73 [0.51, 1.04]
No PAD	572 (2.7)	679 (3.3)	0.85 [0.74, 0.96]
Major Adverse Limb Event	179 (0.8)	222 (0.9)	0.79 [0.61, 1.02]
PAD	78 (2.9)	114 (4.0)	0.55 [0.35, 0.85]
No PAD	101 (0.5)	108 (0.5)	0.90 [0.64, 1.26]
MACE4 or MALE	1369 (5.8)	1693 (7.2)	0.81 [0.73, 0.90]
PAD	234 (8.6)	298 (10.5)	0.71 [0.54, 0.95]
No PAD	1135 (5.4)	1395 (6.7)	0.82 [0.73, 0.92]
MACE3 or MALE	839 (3.5)	1015 (4.3)	0.83 [0.74, 0.93]
PAD	166 (6.1)	228 (8.0)	0.65 [0.48, 0.88]
No PAD	673 (3.2)	787 (3.8)	0.86 [0.76, 0.97]



TOTAL MACE3 OR MALE WITH BEMPEDOIC ACID



TOTAL MACE (3 & 4) OR MALE WITH BEMPEDOIC ACID



SUMMARY

In CLEAR Outcomes:

A significant number of MALE events occurred in those without known PAD at baseline, underscoring the under-diagnosis of PAD in patients at risk

1,624 with symptomatic PAD with ~3/4 “low risk” (e.g. no prior MALE)…Despite this, the risk of MALE event was 2.6%/yr and first MACE-4 event 4.0%/yr in the placebo group

When considering total MACE4+MALE, there were 10.5 events per 100 pt-years in the placebo group

Bempedoic acid reduced first MALE by 36% & total (including recurrent) MALE by 45%

When considering MACE3+MALE and MACE4+MALE there were RRR 29% and 35% respectively translating into absolute reductions of 1.9% per 100 pt-years for both

CONCLUSIONS

Greater awareness and screening for PAD is needed, including in patients with other forms of ASCVD

LDL-C lowering should be a top priority in patients with PAD as a safe and effective means of reducing the risk of MACE and MALE

Combination therapy may be needed for most to achieve low LDL-C levels

Bempedoic acid is effective at reducing MACE & MALE in patients with PAD and should be considered an option for combination therapy (including with statins) that is oral, well tolerated, and does not increase diabetes risk

THANK YOU

Scientific Sessions

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