Supplementary Online Content

Puri R, Nissen SE, Arsenault BJ, et al. Effect of C-reactive protein on lipoprotein(a)-associated cardiovascular risk in optimally treated patients with high-risk vascular disease: a prespecified secondary analysis of the ACCELERATE trial. *JAMA Cardiol.* Published online July 8, 2020. doi:10.1001/jamacardio.2020.2413

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This supplementary material has been provided by the authors to give readers additional information about their work.

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eTable 1. Baseline Characteristics According to Achieved hsCRP Levels

Variable	ACCELERATE N=12092	ACCELERATE Lp(a)-CRP N=10503
Age, yrs	64.4 ± 9.4	64.6 ± 9.4
Male sex, n (%)	9308 (77)	8135 (77.5)
Race, n (%)		
White	9904/12029 (82.3)	8561/10442 (82)
Black	294/12029 (2.4)	275/10442 (2.6)
Asian	1290/12029 (10.7)	1095/10442 (10.5)
Other	541/12029 (4.5)	511/10442 (4.9)
BMI, kg/m^2	30.2 ± 5.7	30.3 ± 5.7
Index diagnosis, n (%)		
ACS	3645 (30.1)	3024 (28.8)
Cerebrovascular disease	1440 (11.9)	1281 (12.2)
Peripheral arterial disease	1674 (13.8)	1471 (14)
Diabetes mellitus with CAD	7792 (64.4)	6838 (65.1)
Hypertension, n (%)	10573 (87.4)	9176 (87.4)
Diabetes (type 1 or 2), n (%)	8236 (68.1)	7240 (68.9)
Prior MI, n (%)	7266/10887 (66.7)	6254/9443 (66.2)
Prior PCI, n (%)	7763/10878 (71.4)	6806/9434 (72.1)
Prior CABG, n (%)	3186/10880 (29.3)	2873/9436 (30.4)
Medications, n (%)		
Statins (any)	11665 (96.5)	10134 (96.5)
High-intensity statins	5557/11947 (46.5)	4845/10373 (46.7)
Anti-hypertensive agents	10564 (87.4)	9151 (87.1)
Aspirin	10007 (82.8)	8805 (83.8)
Evacetrapib	6038 (49.9)	5253 (50.0)

Values are mean±SD or n (%)
BMI: body-mass index; ACS: acute coronary syndrome; CAD: coronary artery disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting

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eTable 2. Biochemistry and Blood Pressure Values at Baseline and Follow-up Within the Overall ACCELERATE hsCRP-Lp(a) Population

Variable	Baseline	Follow-up	*P* Value
LDL (mg/dL)	81.3 ± 27.7	71.4 ± 28.1	< 0.001
HDL (mg/dL)	45.4 ± 11.7	71.5 ± 34.1	< 0.001
hsCRP (mg/L)	1.5 (0.7, 3.3)	1.8 (0.9, 3.9)	< 0.001
Lp(a) (nmol/L)	29.4 (11.2, 109.3)	22.9 (9.5, 98.2)	< 0.001
SBP (mmHg)	131.0 ± 16.6	132.0 ± 13.7	< 0.001

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein(a); SBP = systolic blood pressure

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eTable 3. Clinical Event Rates Within the Overall ACCELERATE hsCRP-Lp(a) Population

Variable	**N (%)**
Death	363 (3.5)
Cardiovascular death	217 (2.1)
*Myocardial infarction	429 (4.1)
*Stroke	159 (1.5)
Coronary revascularization	857 (8.2)
Hospitalization for unstable angina	248 (2.4)
**MACE	714 (6.8)

*Includes fatal and non-fatal events
**MACE is defined as the composite of cardiovascular death, myocardial infarction or stroke

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eTable 4. Relationships Between MACE Stratified According to Achieved hsCRP and Lp(a) Quintiles in the Placebo Group Only

Population	n/N (Kaplan-Meier estimate)	MACE HR (95% CI)	*P* Value
hsCRP <2			
*Lp(a) Q1	37/601 (6.6)	1.0	Ref
Lp(a) Q2	32/606 (6.0)	0.84 (0.52, 1.35)	0.47
Lp(a) Q3	29/585 (5.9)	0.79 (0.48, 1.30)	0.35
Lp(a) Q4	30/582 (5.8)	0.81 (0.50, 1.32)	0.40
Lp(a) Q5	27/595 (4.6)	0.70 (0.42, 1.16)	0.17
hsCRP ≥2			
*Lp(a) Q1	25/449 (6.1)	1.0	Ref
Lp(a) Q2	40/444 (10.8)	1.69 (1.02, 2.79)	0.042
Lp(a) Q3	45/465 (10.9)	1.87 (1.15, 3.06)	0.012
Lp(a) Q4	45/468 (10.7)	1.74 (1.06, 2.84)	0.028
Lp(a) Q5	48/455 (11.8)	1.91 (1.17, 3.11)	0.01
$P_{interaction}$ between Lp(a) quintile and hsCRP for MACE is 0.008			

Hazard ratio (HR) and confidence intervals (CI) are adjusted for age, sex, race, region, diabetes mellitus, smoking, baseline LDL-C, and baseline HDL-C
All hsCRP and Lp(a) levels are time-weighted average; hsCRP measured in mg/L; Lp(a) measured in nmol/L
MACE: cardiovascular death/myocardial infarction/stroke
Median (range) Lp(a) values per Lp(a) quintile: Q1 8.2 (3.1-9.8); Q2 14.6 (9.9-20.3); Q3 30.2 (20.4-46.9); Q4 84.8 (47.0-135.5); Q5 193.9 (135.6-7681)
*Each subsequent quintile (Q) is compared with the first quintile

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eTable 5. Associations Between MACE Stratified According to Achieved hsCRP and Continuous Lp(a) Levels in the Placebo Group Only

	hsCRP <2 HR (95% CI)	*P* Value	hsCRP ≥2 HR (95% CI)	*P* Value	$P_{interaction}$
MACE					
Log Lp(a)	0.93 (0.82, 1.06)	0.30	1.15 (1.02, 1.29)	0.019	0.016

All hsCRP and Lp(a) levels are time-weighted average; hsCRP measured in mg/L; Lp(a) measured in nmol/L
MACE: Cardiovascular death/myocardial infarction/stroke
Hazard ratio (HR) and confidence intervals (CI) are adjusted for age, sex, race, region, diabetes mellitus, smoking, baseline LDL-C, baseline HDL-C

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eTable 6. Relationships Between Primary MACE End Point Stratified According to Achieved hsCRP and Lp(a) Quintiles

Population	n/N (%) (Kaplan-Meier estimate)	MACE HR (95 CI)	*P* Value
Overall hsCRP population			
hsCRP <2	592/5609 (11.2)	1.0	Ref
hsCRP ≥2	712/4894 (16.0)	1.31 (1.17, 1.47)	<0.001
Overall Lp(a) population			
Lp(a) <median	611/5251 (12.6)	1.0	Ref
Lp(a) ≥median	693/5252 (14.3)	1.10 (0.98, 1.23)	0.092
hsCRP <2			
*Lp(a) Q1	112/1154 (10.1)	1.0	Ref
Lp(a) Q2	111/1129 (10.6)	1.00 (0.77, 1.31)	0.99
Lp(a) Q3	117/1113 (11.3)	1.09 (0.83, 1.42)	0.54
Lp(a) Q4	109/1103 (10.6)	1.00 (0.76, 1.31)	0.97
Lp(a) Q5	143/1110 (13.5)	1.30 (1.00, 1.67)	0.046
hsCRP ≥2			
*Lp(a) Q1	112/946 (13.1)	1.0	Ref
Lp(a) Q2	128/972 (14.4)	1.08 (0.84, 1.40)	0.54
Lp(a) Q3	139/988 (15.7)	1.20 (0.94, 1.55)	0.15
Lp(a) Q4	168/998 (18.9)	1.38 (1.08, 1.77)	0.010
Lp(a) Q5	165/990 (17.9)	1.40 (1.09, 1.79)	0.008
$P_{interaction}$ between Lp(a) quintile and hsCRP ≥2 vs. <2 for MACE is 0.39			

Hazard ratio (HR) and confidence intervals (CI) are adjusted for age, sex, race, region, diabetes mellitus, smoking, baseline LDL-C, baseline HDL-C and randomization/treatment group

All hsCRP and Lp(a) levels are time-weighted average; hsCRP measured in mg/L; Lp(a) measured in nmol/L

Primary MACE endpoint:

Cardiovascular death/myocardial infarction/stroke/coronary revascularization/hospitalization for unstable angina

Median (range) Lp(a) values per Lp(a) quintile: Q1 8.2 (2.2-8.4); Q2 11.1 (8.5-15.7); Q3 22.9 (15.8-37.5); Q4 71.7 (37.6-125.4); Q5 183.4 (125.5-7681)

*Each subsequent quintile (Q) is compared with the first quintile

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eTable 7. Associations Between Primary MACE End Point Stratified According to Achieved hsCRP and Continuous Lp(a) Levels

	hsCRP <2 HR (95% CI)	*P* Value	hsCRP ≥2 HR (95% CI)	*P* Value	$P_{interaction}$
MACE					
Logarithm of Lp(a)	1.06 (1.00, 1.14)	0.065	1.11 (1.05, 1.18)	0.001	0.46

Hazard ratio (HR) and confidence intervals (CI) are adjusted for age, sex, race, region, diabetes mellitus, smoking, baseline LDL-C, baseline HDL-C, and randomization/treatment group
All hsCRP and Lp(a) levels are time-weighted average; hsCRP measured in mg/L; Lp(a) measured in nmol/L
Primary MACE endpoint:
Cardiovascular death/myocardial infarction/stroke/coronary revascularization/hospitalization for unstable angina

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eTable 8. Relationships Between hsCRP and Lp(a) as Continuous Variables Upon MACE

Interaction (*)	**Univariate *P*-$_{interaction}$**	**Multivariable *P*-$_{interaction}$**
Continuous (log)hsCRP*Lp(a) quintile	0.014	0.012
Continuous Lp(a)*hsCRP quintile	0.068	0.10

Multivariable model djusted for age, sex, race, region, diabetes mellitus, smoking, baseline LDL-C, baseline HDL-C, and randomization/treatment group
All hsCRP and Lp(a) levels are time-weighted average; hsCRP measured in mg/L; Lp(a) measured in nmol/L
MACE: Cardiovascular death/myocardial infarction/stroke

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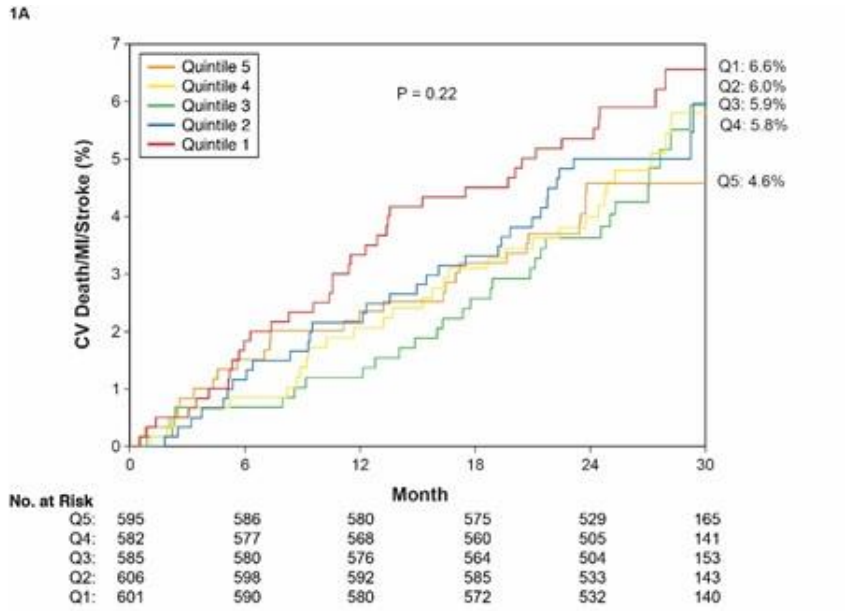
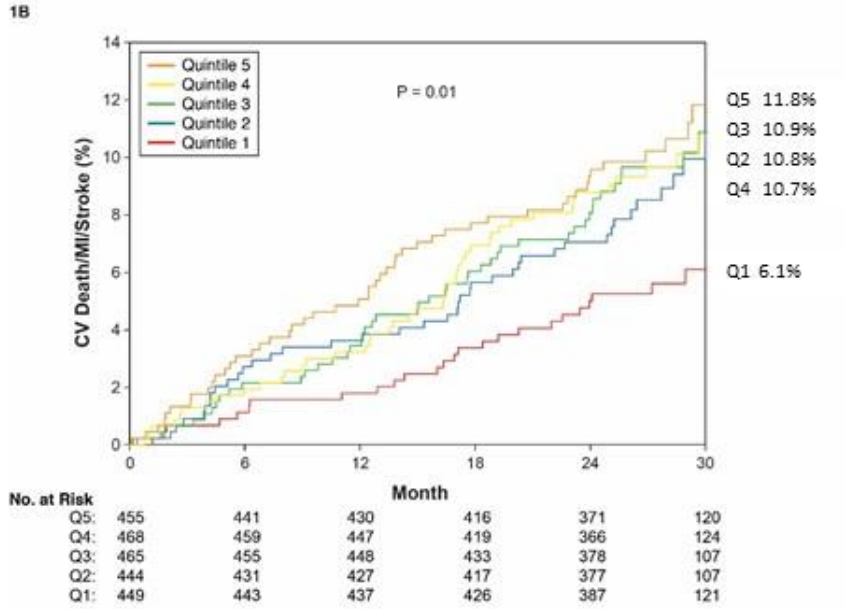
eFigure 1. Cumulative Incidence of MACE Over Time Stratified According to Lp(a) Quintiles in the Setting of hsCRP Levels <2 mg/L (A) or ≥2 mg/L (B)

This represents the population that did not receive evacetrapib (ie, the placebo group of ACCELERATE).





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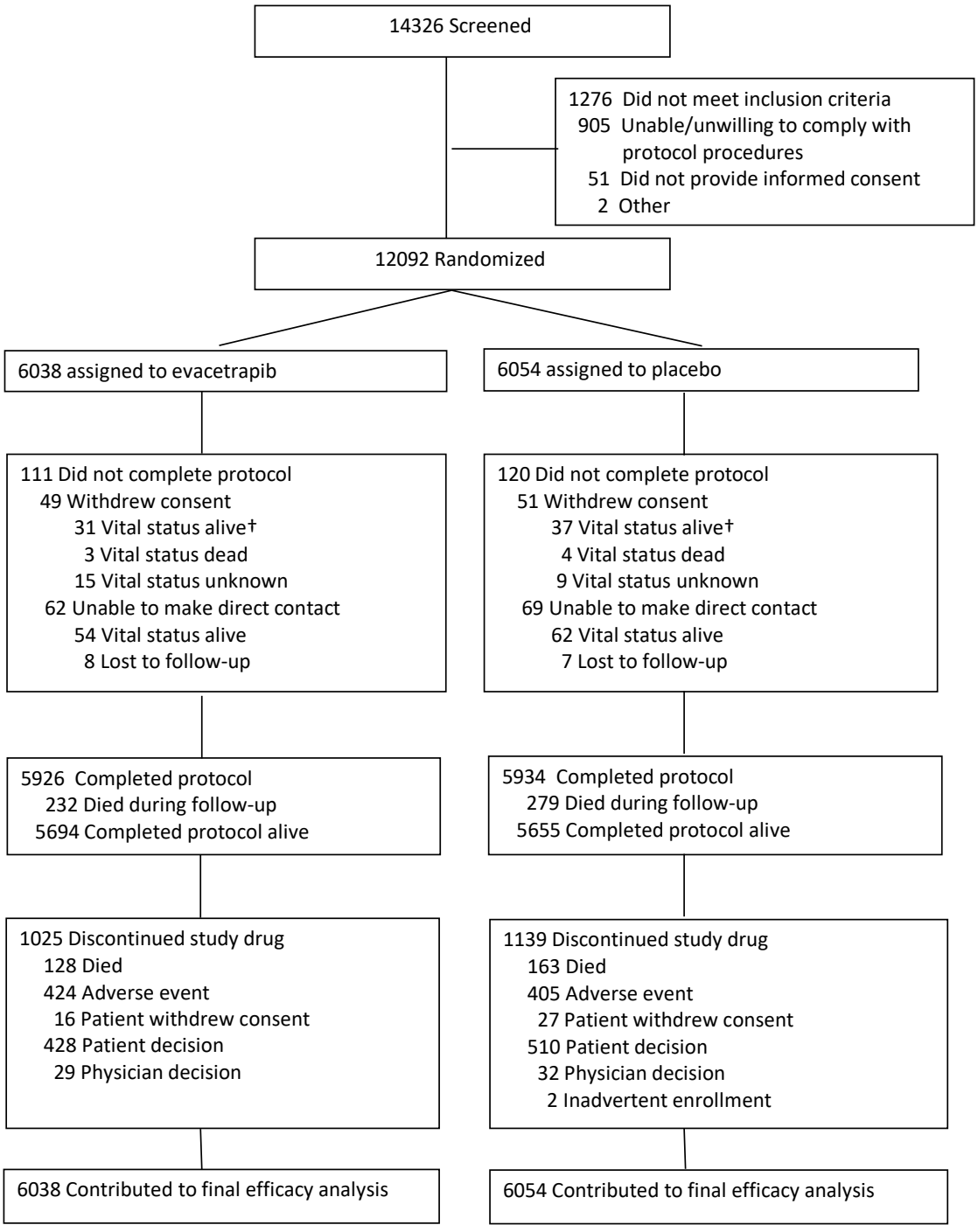
eFigure 2. CONSORT Diagram



† Verification of alive status based on absence in the death registry

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