AMARIN

Discussion of Primary REDUCE-IT™ Trial Results as Presented on November 10, 2018 at Scientific Sessions of American Heart Association and Simultaneously Published in *The New England Journal of Medicine* (NEJM)

November 10, 2018

NASDAQ: **AMRN**

Pure EPA

Vascepa®

(icosapent ethyl)

NEJM article available at
nejm.org/doi/full/10.1056/NEJMoa1812792

Forward-Looking Statements and Disclaimer

Forward-looking statements

This presentation contains forward-looking statements, such as those relating to the commercial potential of Vascepa®, clinical and regulatory efforts and timelines, potential FDA approvals, intellectual property, cash flow, and other statements that are predictive in nature and that depend upon or refer to future events or conditions. These statements involve known and unknown risks, uncertainties and other factors that can cause actual results to differ materially. For example, as with any study result, further REDUCE-IT data assessment and data release by Amarin and FDA could yield additional useful information to inform greater understanding of the trial outcome. Investors should not place undue reliance on primary data or forward-looking statements, which speak only as of the presentation date of this presentation. Please refer to the "Risk Factors" section in Amarin's most recent Form 10-Q filed with the SEC and cautionary statements outlined in recent press releases for more complete descriptions of risks in an investment in Amarin. Comments in this presentation are current as of today, November 10, 2018.

Presentation is for investors (not drug promotion)

This presentation is intended for communication with investors only.

Nothing in this presentation should be construed as promoting the use of Amarin's product or product candidates.

Presentation Overview

Primary results of REDUCE-IT™ cardiovascular outcomes trial as presented earlier today (no new data)

Brief overview of prior studies relevant to the REDUCE-IT outcome

Brief overview of prior studies of mechanistic effects of icosapent ethyl, the unique active ingredient of Vascepa®

Not discussed: commercial, regulatory and other activities of Amarin

- See Amarin's most recent quarterly report and Amarin's investor slide deck for discussion of such operational and commercial matters

This presentation is being recorded

Presenting in this Investor Presentation

Presenting primary results of REDUCE-IT study:

- Steven Ketchum, PhD, Amarin's Chief Scientific Officer
- Rebecca Juliano, PhD, Amarin's VP Clinical R&D

Available for comment and Q&A after the scientific presentation:

- Michael Miller, MD
- Robert Busch, MD
- Craig Granowitz, MD, PhD, Amarin's Chief Medical Officer
- John Thero, Amarin's President and Chief Executive Officer

Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

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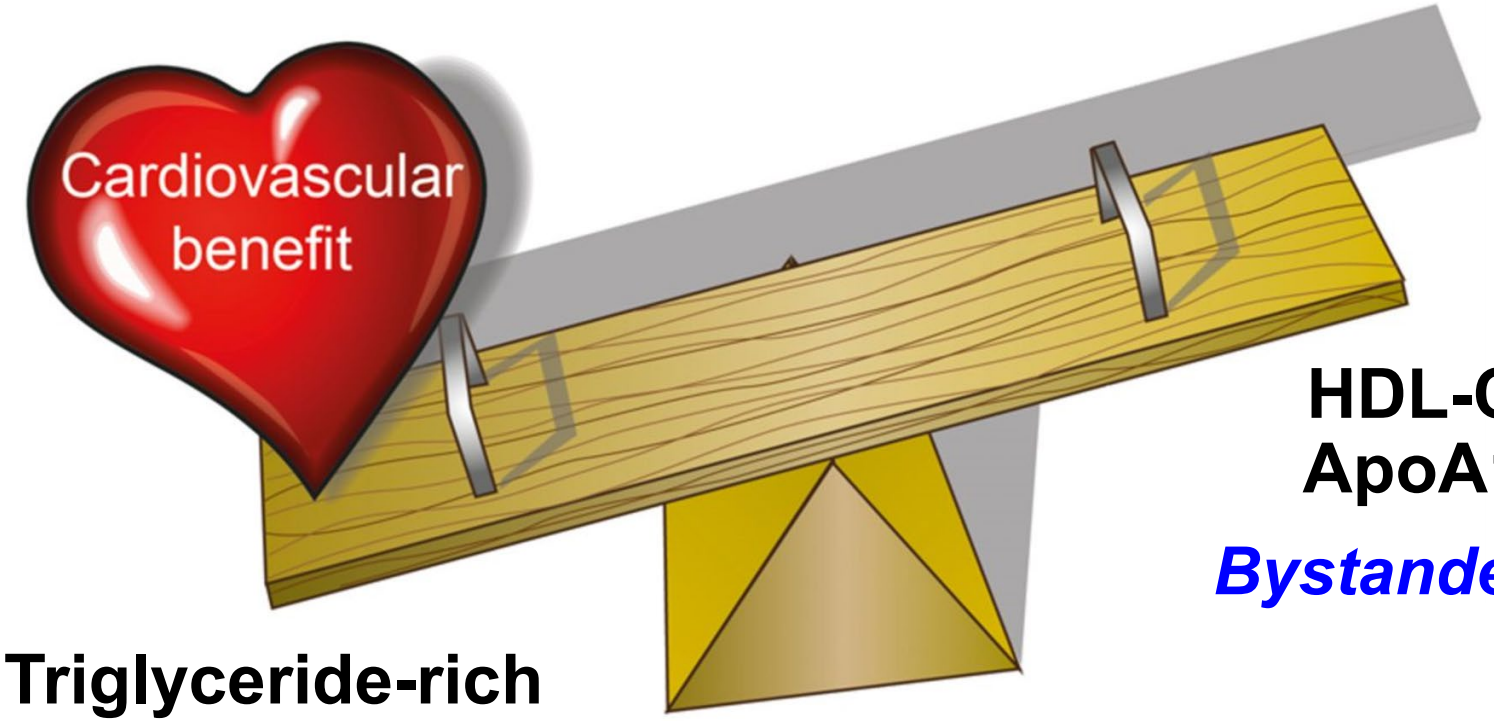
on Behalf of the REDUCE-IT Investigators

Amarin's drug **Vascepa®**, as studied in REDUCE-IT™, is referenced i55n these scientific slides by its non-brand name **icosapent ethyl**

Disclosures

- **Dr. Deepak L. Bhatt** discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); **Research Funding**: Abbott, **Amarin**, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda.
- **This presentation includes off-label and/or investigational uses of drugs.**
- **REDUCE IT was sponsored by Amarin Pharma, Inc.**

Triglycerides a Causal Risk Factor?



Triglyceride-rich lipoproteins
ApoC3

Causal risk factors?

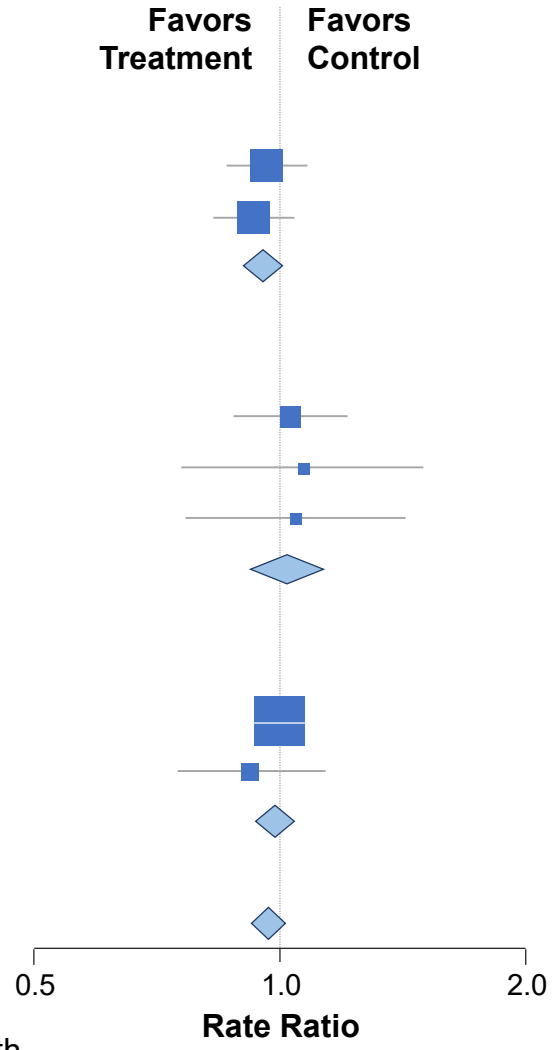
HDL-C
ApoA1

Bystanders?

Adapted with permission from Libby P. Triglycerides on the rise: should we swap seats on the seesaw? *Eur Heart J*. 2015;36:774-776.

Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

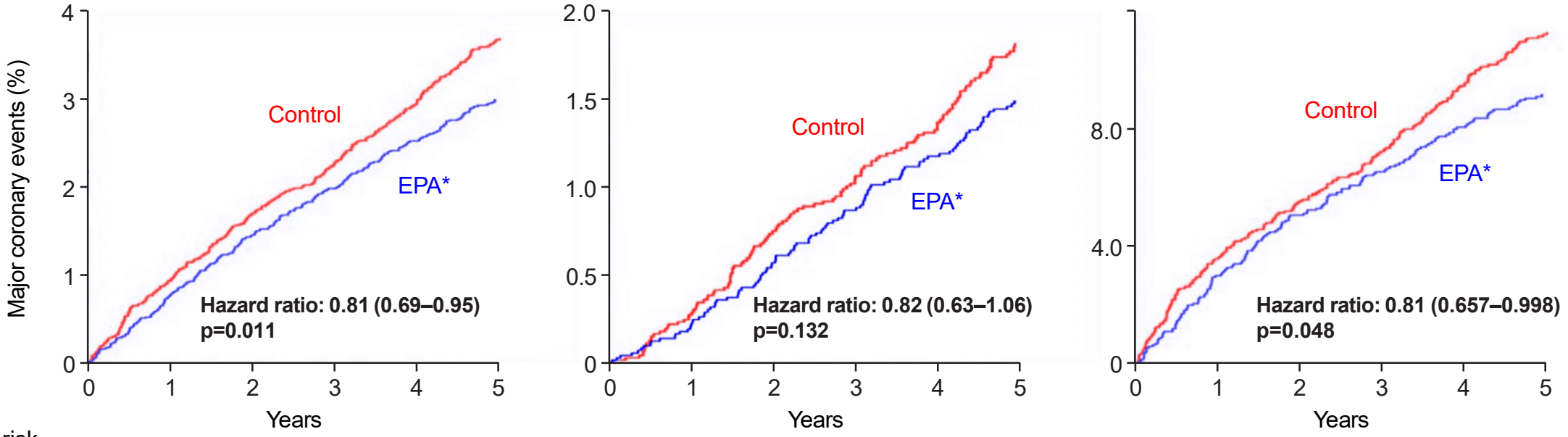
Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87–1.08)
Coronary heart disease	1301 (3.3)	1394 (3.6)	0.93 (0.83–1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90–1.01)
			P=.12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88–1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76–1.51)
Unclassified/other	142 (0.4)	135 (0.3)	1.05 (0.77–1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93–1.13)
			P=.60
Revascularization			
Coronary	3044 (9.3)	3040 (9.3)	1.00 (0.93–1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75–1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94–1.04)
			P=.60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93–1.01)
			P=.10



Adapted with permission‡ from Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77917 individuals. *JAMA Cardiol.* 2018;3:225-234. [‡https://creativecommons.org/licenses.org/by-nc/4.0/]

JELIS Suggests CV Risk Reduction with EPA in Japanese Hypercholesterolemic Patients

Kaplan-Meier Estimates of Incidence of Coronary Events



Numbers at risk						
Control group	9319	8931	8671	8433	8192	7958
Treatment group	9326	8929	8658	8389	8153	7924

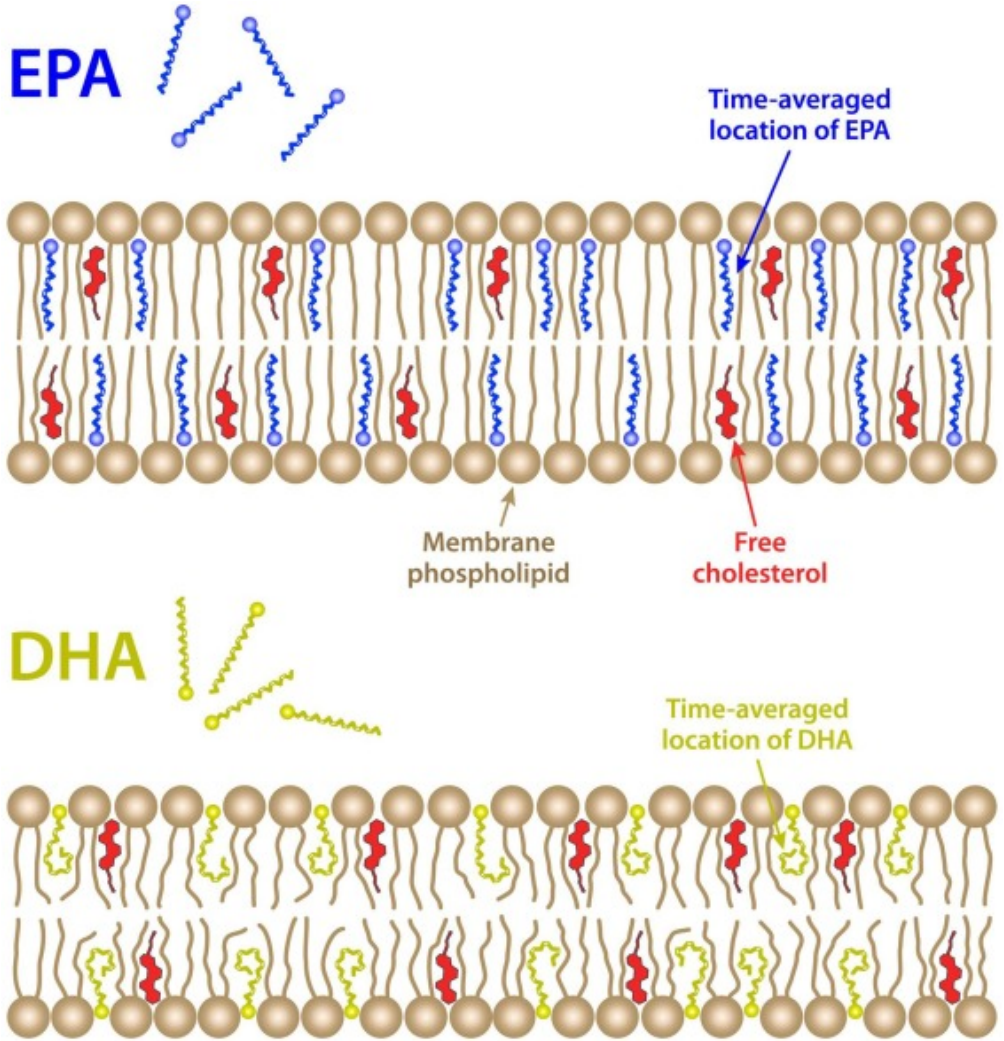
7478	7204	7103	6841	6678	6508
7503	7210	7020	6823	6649	6482

1841	1727	1658	1592	1514	1450
1823	1719	1638	1566	1504	1442

*1.8 g/day

Adapted with permission from Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet.* 2007;369:1090-1098.

EPA and DHA Have Differing Effects on Cellular Membranes



Reprinted with permission* from Sherratt SCR, Mason RP. Eicosapentaenoic acid and docosahexaenoic acid have distinct membrane locations and lipid interactions as determined by X-ray diffraction. *Chem Phys Lipids*. 2018;212:73-79. [*https://creativecommons.org/licenses.org/by-nc/4.0/]

Key Inclusion Criteria – REDUCE-IT

1. Age ≥45 years with established CVD (Secondary Prevention Cohort) *or* ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)

2. Fasting TG levels ≥150 mg/dL and <500 mg/dL*
   - As provided in the protocol, ~10% of patients were enrolled with TG <150 mg/dL

3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

*Due to the variability of triglycerides, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

Inclusion Criteria for Secondary Prevention Cohort

One or more of the following:

1. Documented coronary artery disease
   - Multi vessel CAD (≥50% stenosis in ≥2 major epicardial coronary arteries – with or without antecedent revascularization
   - Prior MI
   - Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome with ST-segment deviation or biomarker positivity

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2. Documented cerebrovascular or carotid disease
   - Prior ischemic stroke
   - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis
   - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis
   - History of carotid revascularization

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   - Prior ischemic stroke
   - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis
   - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis
   - History of carotid revascularization
3. Documented peripheral artery disease
   - Ankle-brachial index <0.9 with symptoms of intermittent claudication
   - History of aorto-iliac or peripheral artery intervention

Inclusion Criteria for Primary Prevention Cohort

1. Diabetes mellitus requiring medication AND

Patients with diabetes and CVD are counted under Secondary Prevention Cohort

Inclusion Criteria for Primary Prevention Cohort

1. Diabetes mellitus requiring medication AND
2. ≥50 years of age AND

Patients with diabetes and CVD are counted under Secondary Prevention Cohort

Inclusion Criteria for Primary Prevention Cohort

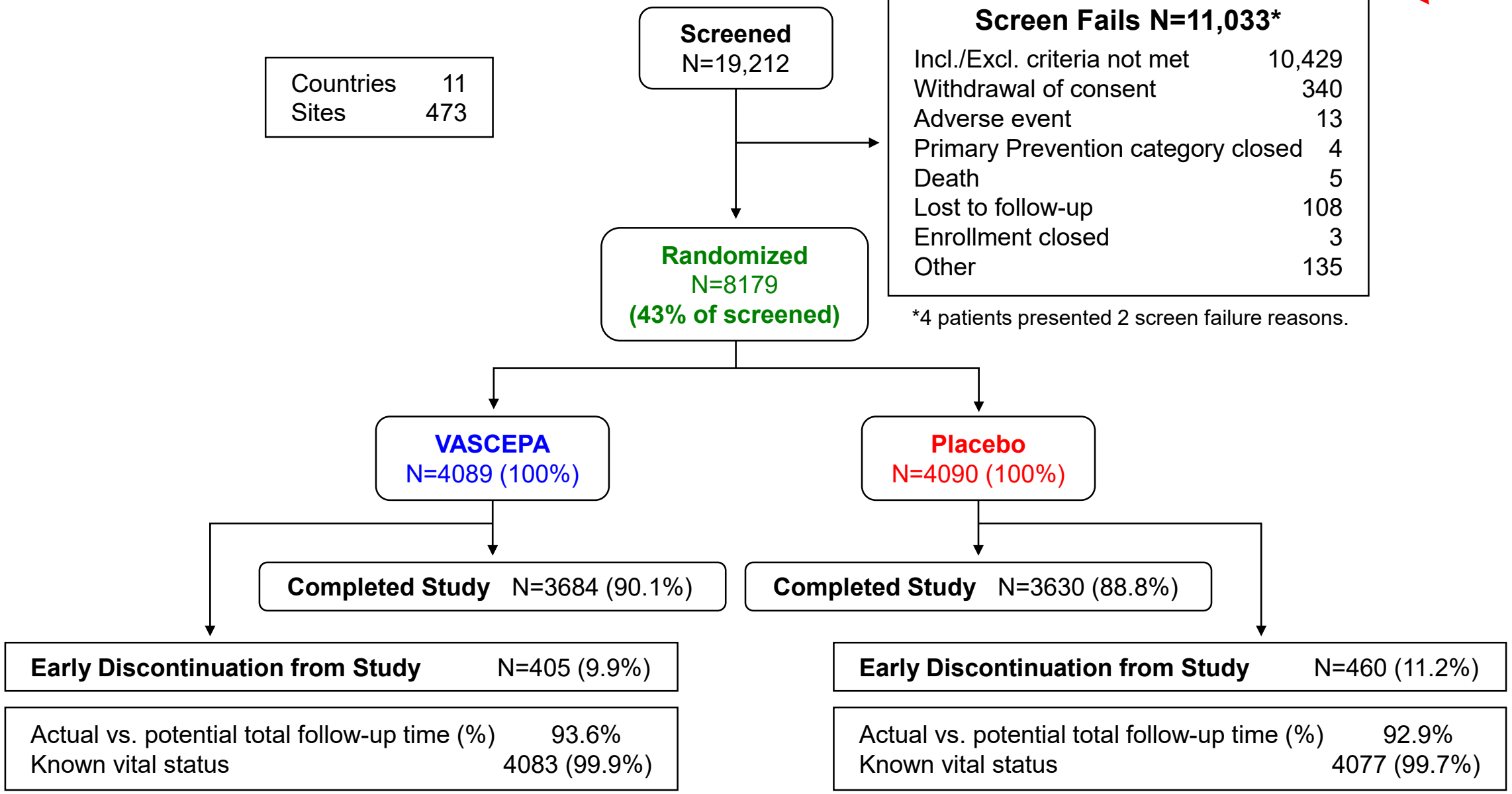
1. Diabetes mellitus requiring medication AND
2. ≥50 years of age AND
3. ≥1 additional risk factor for CVD
   - Men ≥55 years and women ≥65 years
   - Cigarette smoker or stopped smoking within 3 months
   - Hypertension (≥140 mmHg systolic OR ≥90 mmHg diastolic) or on antihypertensive medication;
   - HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women
   - hsCRP >3.0 mg/L
   - Renal dysfunction: Creatinine clearance >30 and <60 mL/min
   - Retinopathy
   - Micro- or macroalbuminuria
   - ABI <0.9 without symptoms of intermittent claudication

Patients with diabetes and CVD are counted under Secondary Prevention Cohort

Key Exclusion Criteria

1. Severe (NYHA class IV) heart failure
2. Severe liver disease
3. History of pancreatitis
4. Hypersensitivity to fish and/or shellfish

REDUCE-IT CONSORT Diagram



Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Median trial follow up duration was 4.9 years.

REDUCE-IT Study PI and Committees

Global Principal Investigator and Steering Committee Chair

Deepak L. Bhatt MD, MPH, Professor of Medicine at Harvard Medical School, Executive Director of Interventional Cardiovascular Programs at Brigham and Women's Hospital Heart & Vascular Center, and the Global Principal Investigator and Steering Committee Chair of REDUCE-IT

Steering Committee

Deepak L. Bhatt MD, MPH (Chair and Global Principal Investigator), Christie M. Ballantyne MD, Eliot A. Brinton MD, Terry A. Jacobson MD, Michael Miller MD, Ph. Gabriel Steg MD, Jean-Claude Tardif MD

Data Monitoring Committee

Brian Olshansky MD (Chair), Mina Chung MD, Al Hallstrom PhD, Lesly A. Pearce MS (non-voting independent statistician)

Independent Statistical Center Support for Data Monitoring Committee: Cyrus Mehta PhD, Rajat Mukherjee PhD

Clinical Endpoint Committee

C. Michael Gibson MD, MS (Chair), Anjan K. Chakrabarti MD, MPH, Eli V. Gelfand MD, Robert P. Giugliano MD, SM, Megan Carroll Leary MD, Duane S. Pinto MD, MPH, Yuri B. Pride MD

Key Baseline Characteristics

	VASCEPA (N=4089)	Placebo (N=4090)
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)
Female, n (%)	1162 (28.4%)	1195 (29.2%)
Non-White, n (%)	398 (9.7%)	401 (9.8%)
Westernized Region, n (%)	2906 (71.1%)	2905 (71.0%)
CV Risk Category, n (%)		
Secondary Prevention Cohort	2892 (70.7%)	2893 (70.7%)
Primary Prevention Cohort	1197 (29.3%)	1197 (29.3%)
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)
Statin Intensity, n (%)		
Low	254 (6.2%)	267 (6.5%)
Moderate	2533 (61.9%)	2575 (63.0%)
High	1290 (31.5%)	1226 (30.0%)
Type 2 Diabetes, n (%)	2367 (57.9%)	2363 (57.8%)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)
LDL-C (mg/dL), Median (Q1-Q3)	74.0 (61.5 - 88.0)	76.0 (63.0 - 89.0)
Triglycerides Category		
<150 mg/dL	412 (10.1%)	429 (10.5%)
150 to <200 mg/dL	1193 (29.2%)	1191 (29.1%)
≥200 mg/dL	2481 (60.7%)	2469 (60.4%)

Notes: Well represented male/female for a CVOT; mostly Westernized; intended mix of secondary/primary prevention; 58% with diabetes; all patients on statin therapy, mostly high dose statins, limited use of other LDL-C lowering agents with LDL-C well-controlled

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Effects on Biomarkers from Baseline to Year 1

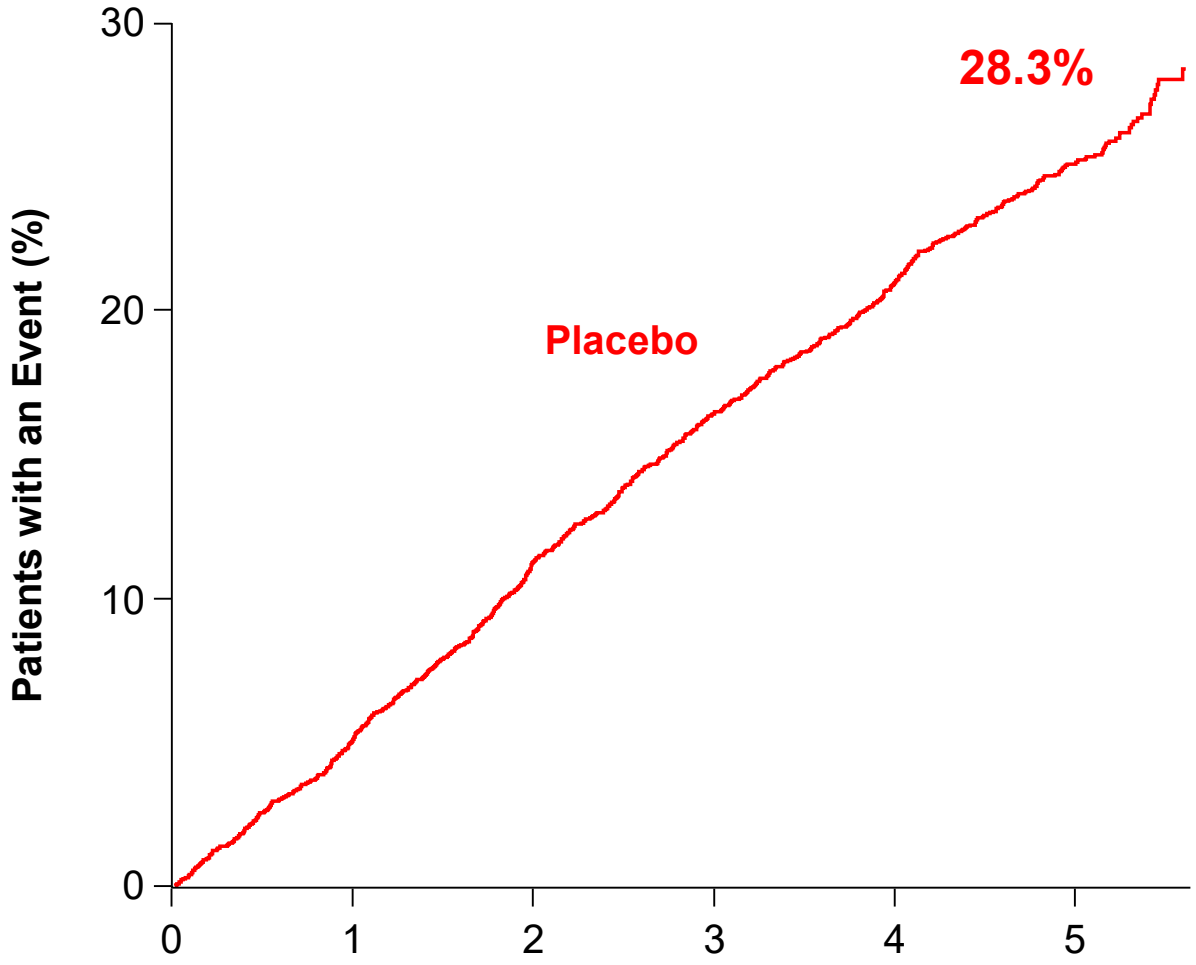
	VASCEPA (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	**Baseline**	**Year 1**	**Baseline**	**Year 1**	**Absolute Change from Baseline**	**% Change from Baseline**	**% Change P-value**
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

*Apo B and hsCRP were measured at Year 2.

Notes: LDL-C well controlled with median baseline at 75 mg/dL; TG levels moderately elevated with median baseline at 216 mg/dL at one-year ~36% of patients in the Vascepa group had TG <150 mg/dL

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Notes: Median follow-up was 4.9 years

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

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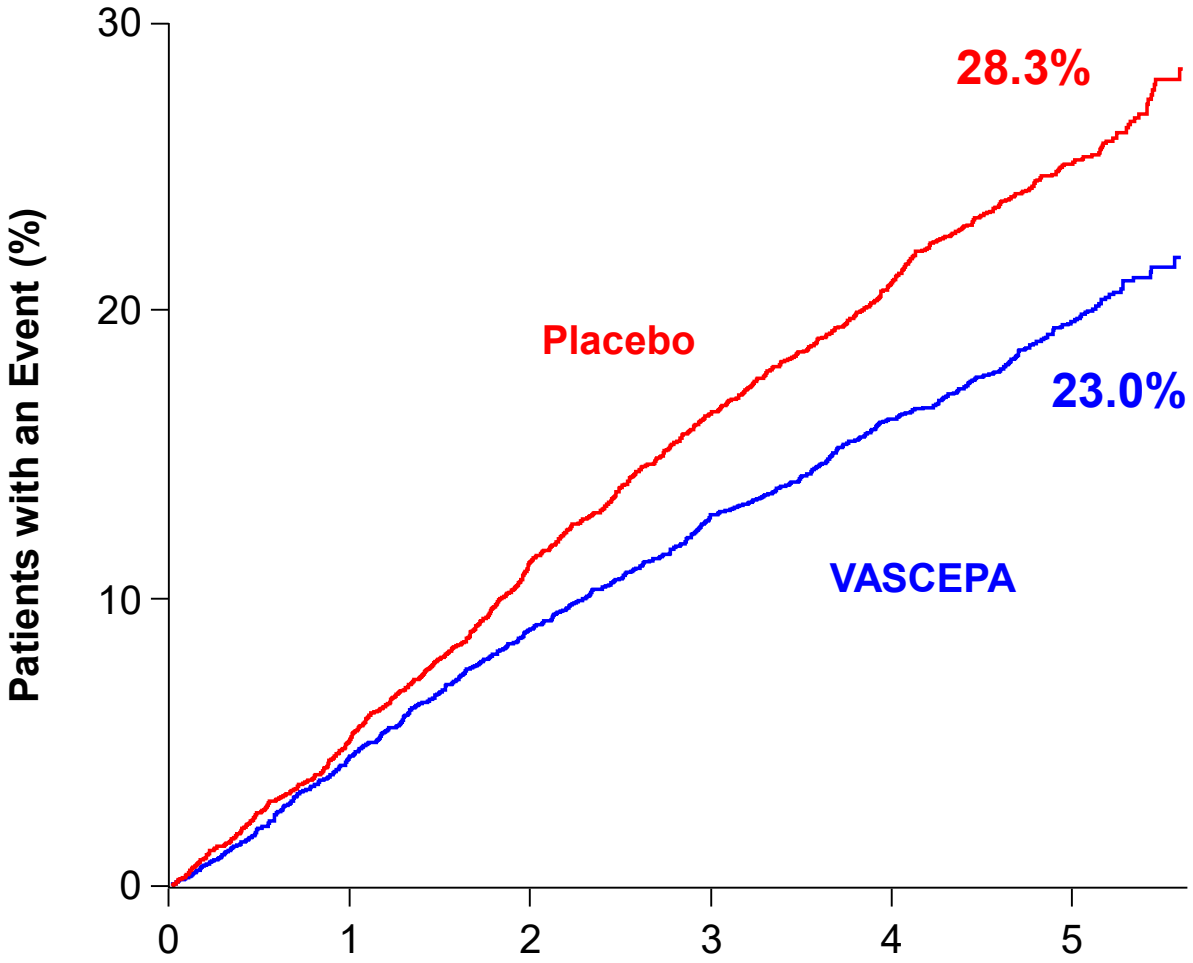

Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

Notes: Median follow-up was 4.9 years
The CV event curve for VASCEPA visually separated from the placebo event curve at approx. 1 year and continued to separate throughout the follow-up period

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

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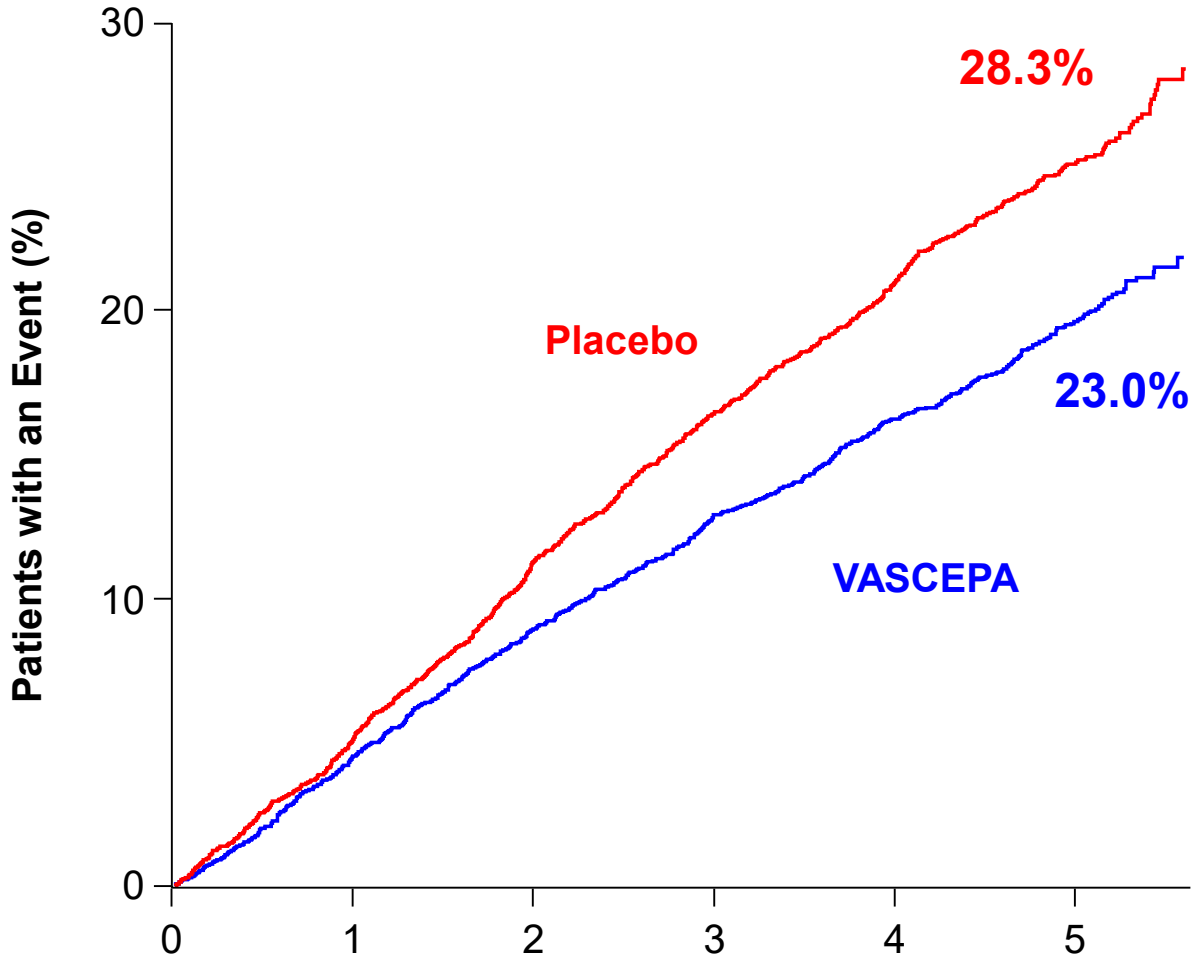

Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

RRR = 24.8%

ARR = 4.8%

NNT = 21 (95% CI, 15–33)

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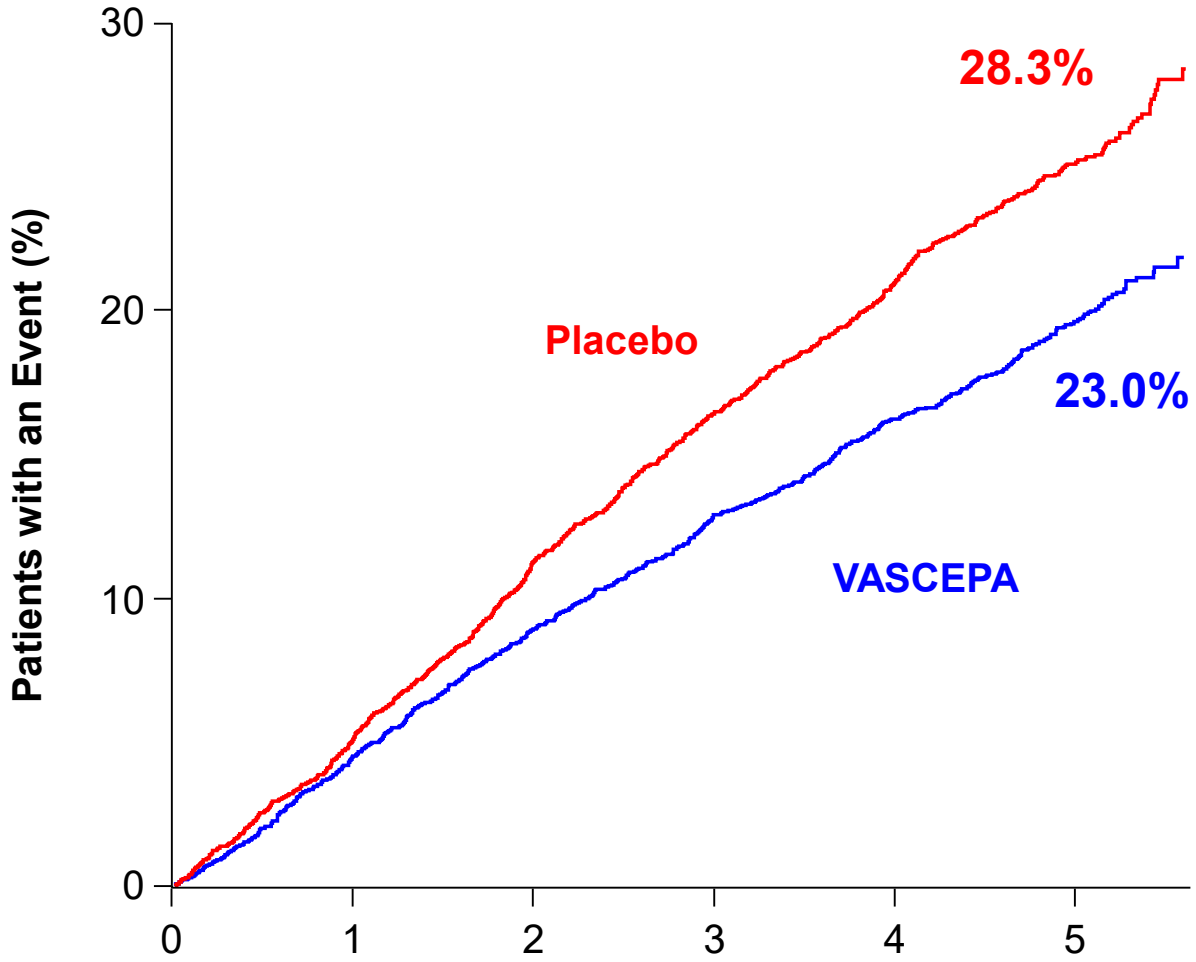

Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

RRR = 24.8%

ARR = 4.8%

NNT = 21 (95% CI, 15–33)

P=0.00000001

Notes: Median follow-up was 4.9 years

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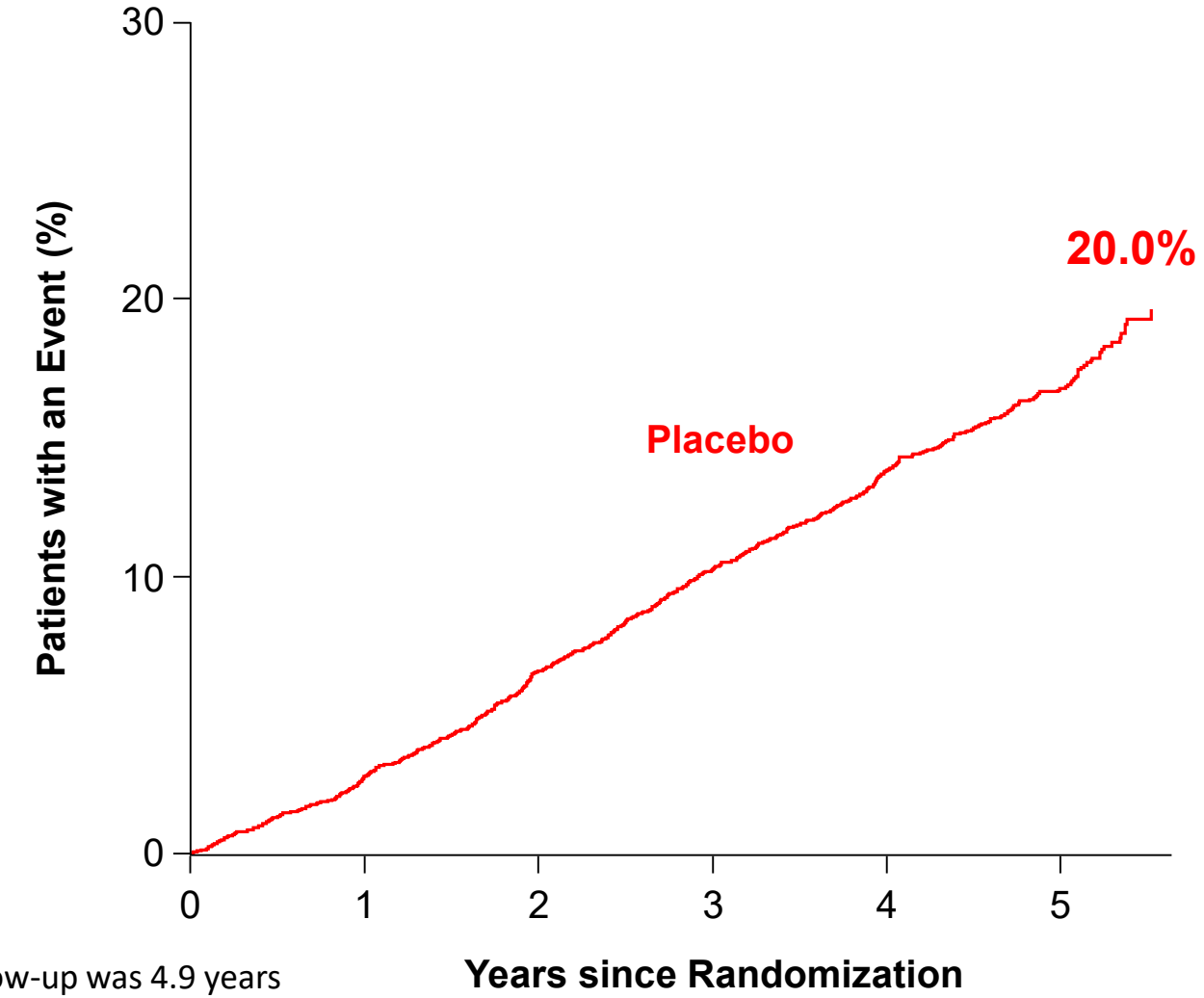
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

Key Secondary End Point:
CV Death, MI, Stroke



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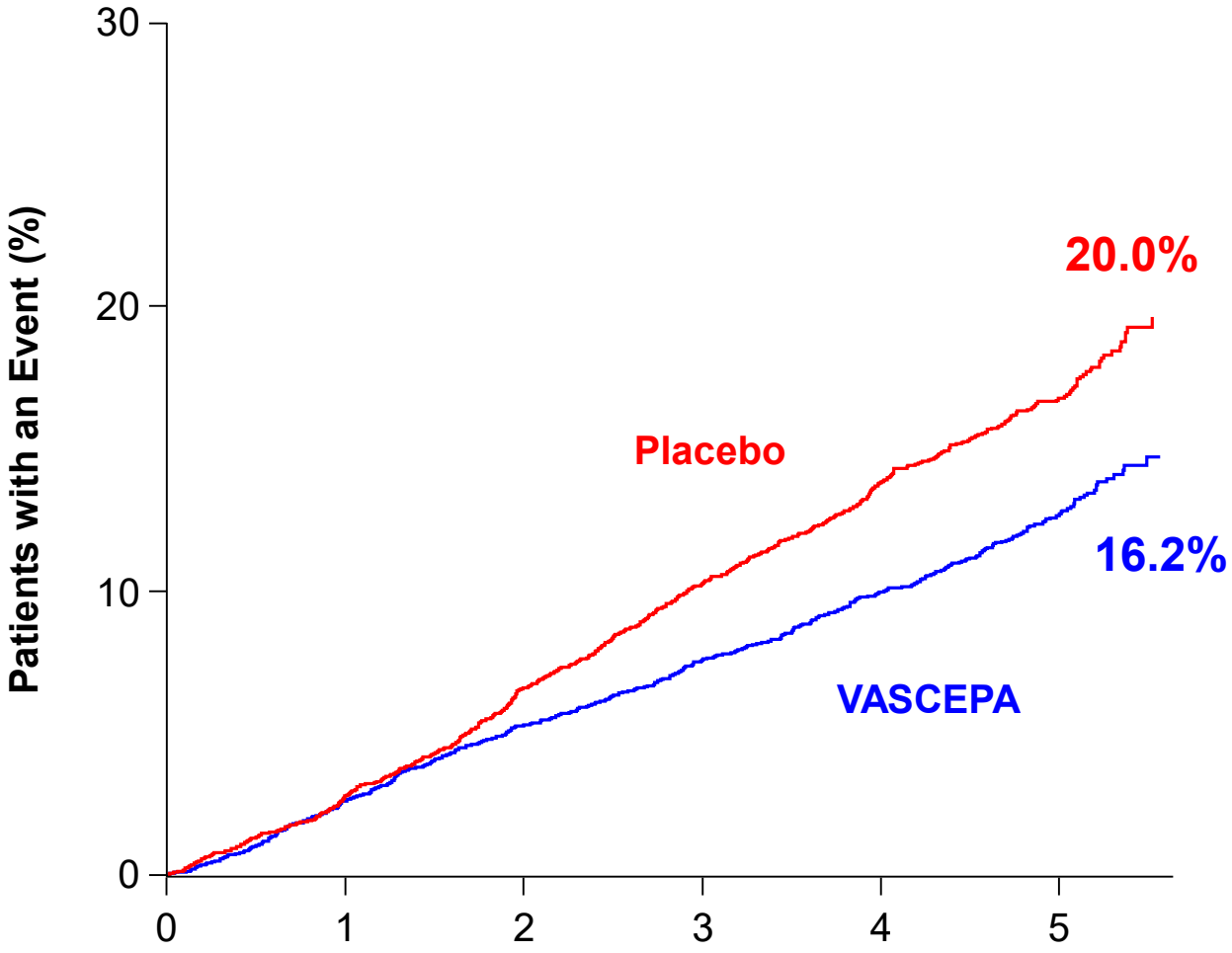
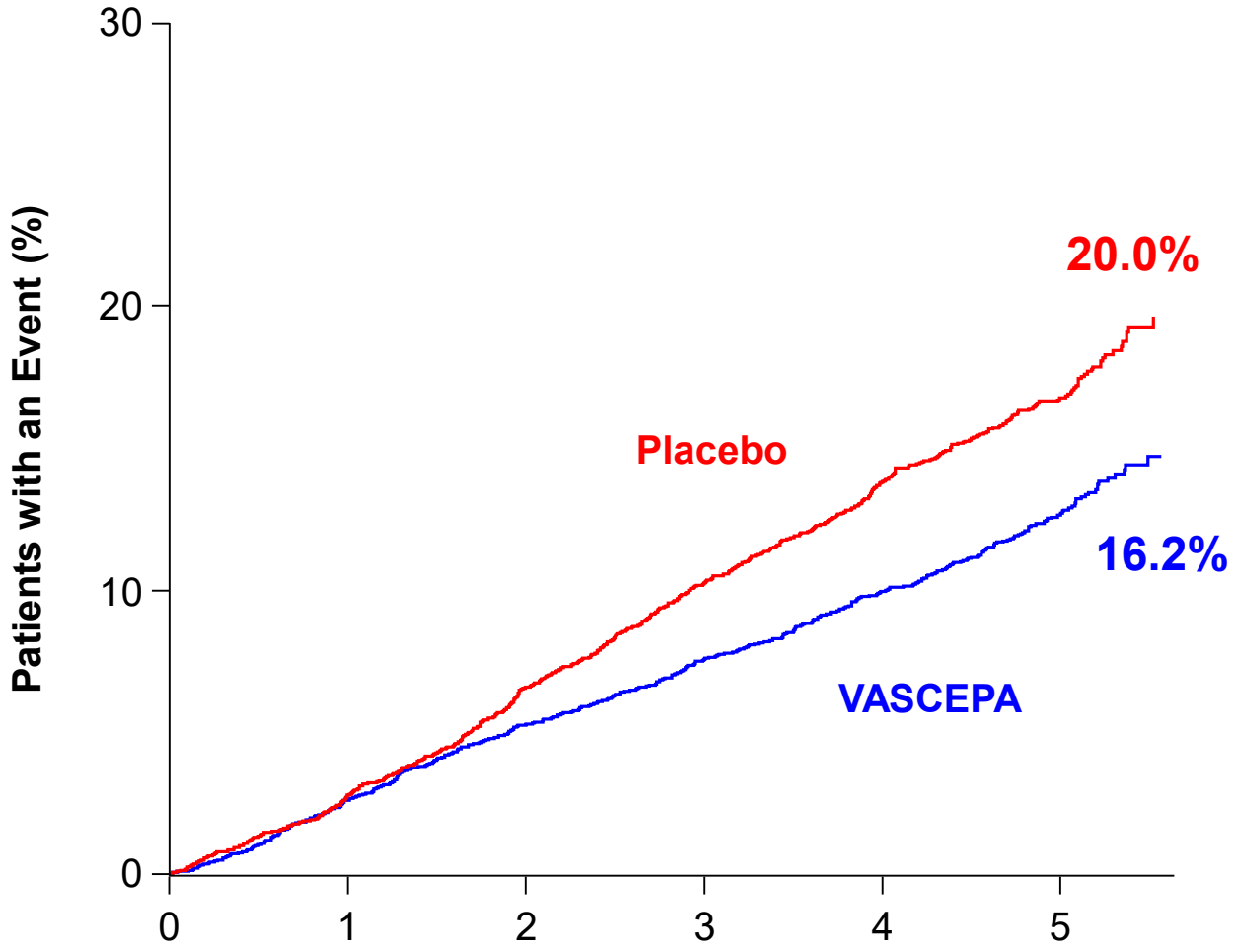


Hazard Ratio, 0.74
(95% CI, 0.65–0.83)

Notes: Median follow-up was 4.9 years
The CV event curve for VASCEPA visually separated from the placebo event curve at approx. 1.75 years and continued to separate throughout the follow-up period

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)

RRR = 26.5%

ARR = 3.6%

NNT = 28 (95% CI, 20–47)

Notes: Median follow-up was 4.9 years

The CV event curve for VASCEPA visually separated from the placebo event curve at approx. 1.75 years and continued to separate throughout the follow-up period

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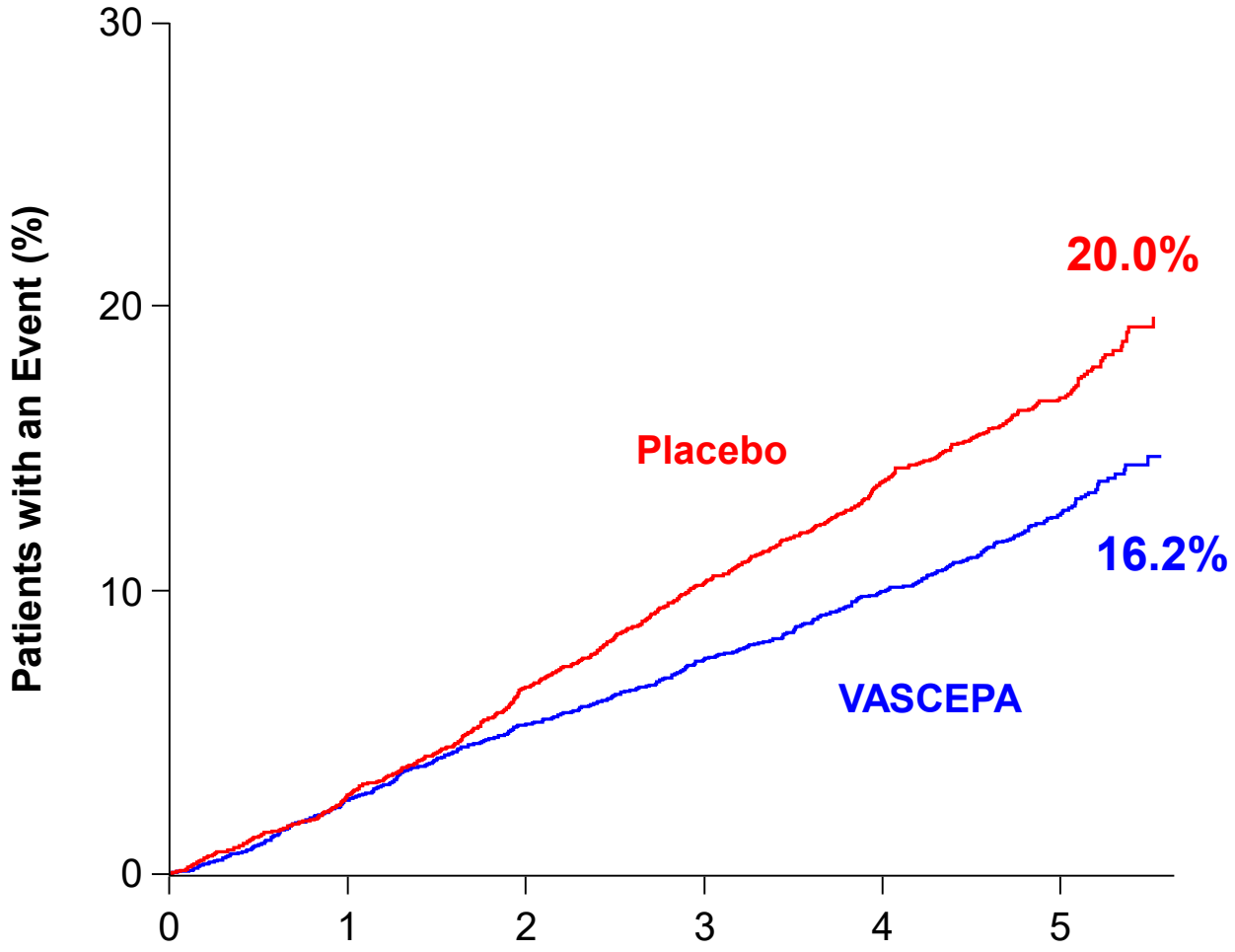
Key Secondary End Point:
CV Death, MI, Stroke

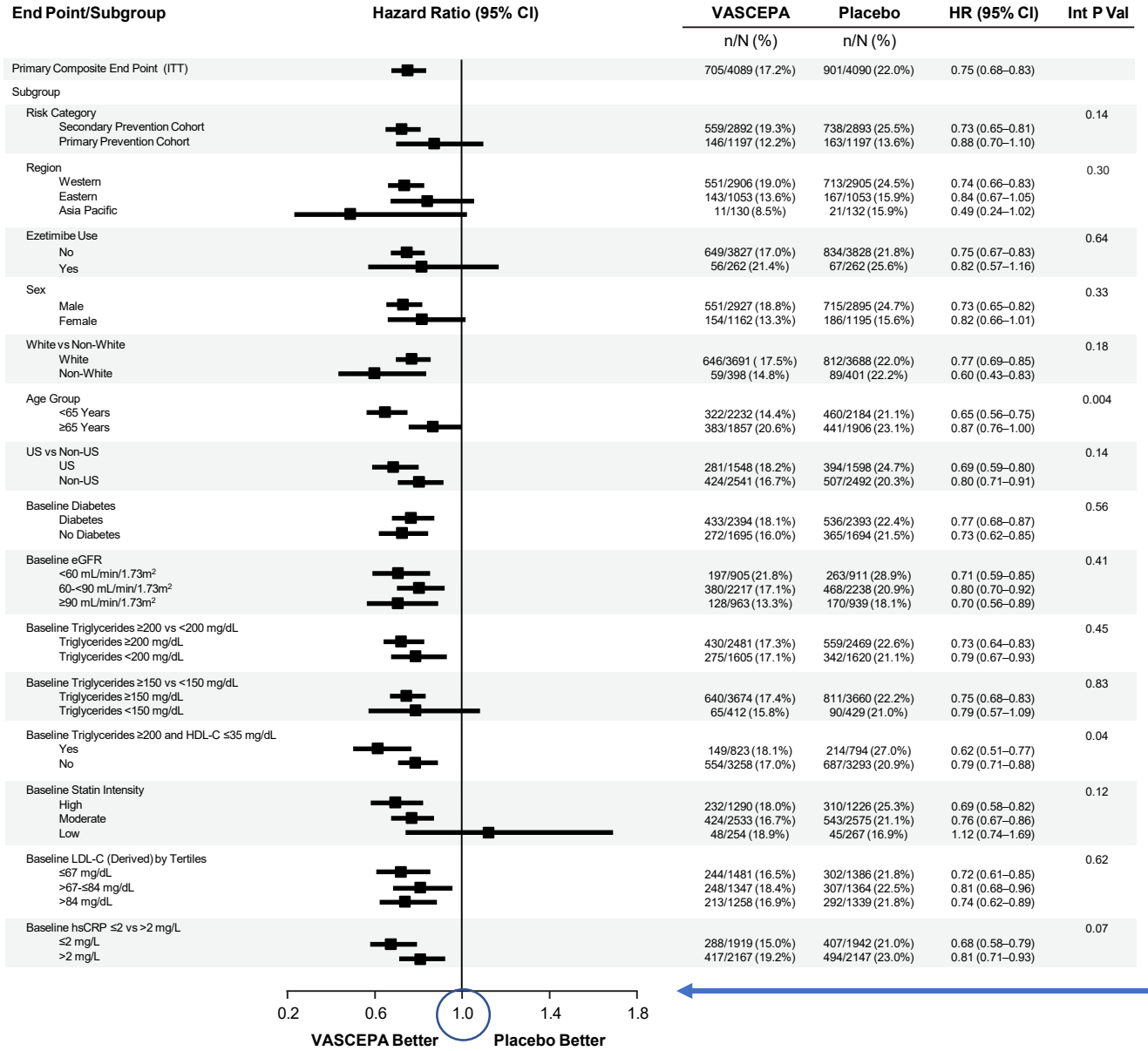


Hazard Ratio, 0.74
(95% CI, 0.65–0.83)
RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
P=0.0000006

Notes: Median follow-up was 4.9 years
The CV event curve for VASCEPA visually separated from the placebo event curve at approx. 1.75 years and continued to separate throughout the follow-up period

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

Primary End Point in Subgroups



End Point/Subgroup	VASCEPA n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Primary Composite End Point (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	
Subgroup				
Risk Category				0.14
Secondary Prevention Cohort	559/2892 (19.3%)	738/2893 (25.5%)	0.73 (0.65–0.81)	
Primary Prevention Cohort	146/1197 (12.2%)	163/1197 (13.6%)	0.88 (0.70–1.10)	
Region				0.30
Western	551/2906 (19.0%)	713/2905 (24.5%)	0.74 (0.66–0.83)	
Eastern	143/1053 (13.6%)	167/1053 (15.9%)	0.84 (0.67–1.05)	
Asia Pacific	11/130 (8.5%)	21/132 (15.9%)	0.49 (0.24–1.02)	
Ezetimibe Use				0.64
No	649/3827 (17.0%)	834/3828 (21.8%)	0.75 (0.67–0.83)	
Yes	56/262 (21.4%)	67/262 (25.6%)	0.82 (0.57–1.16)	
Sex				0.33
Male	551/2927 (18.8%)	715/2895 (24.7%)	0.73 (0.65–0.82)	
Female	154/1162 (13.3%)	186/1195 (15.6%)	0.82 (0.66–1.01)	
White vs Non-White				0.18
White	646/3691 (17.5%)	812/3688 (22.0%)	0.77 (0.69–0.85)	
Non-White	59/398 (14.8%)	89/401 (22.2%)	0.60 (0.43–0.83)	
Age Group				0.004
<65 Years	322/2232 (14.4%)	460/2184 (21.1%)	0.65 (0.56–0.75)	
≥65 Years	383/1857 (20.6%)	441/1906 (23.1%)	0.87 (0.76–1.00)	
US vs Non-US				0.14
US	281/1548 (18.2%)	394/1598 (24.7%)	0.69 (0.59–0.80)	
Non-US	424/2541 (16.7%)	507/2492 (20.3%)	0.80 (0.71–0.91)	
Baseline Diabetes				0.56
Diabetes	433/2394 (18.1%)	536/2393 (22.4%)	0.77 (0.68–0.87)	
No Diabetes	272/1695 (16.0%)	365/1694 (21.5%)	0.73 (0.62–0.85)	
Baseline eGFR				0.41
<60 mL/min/1.73m^2	197/905 (21.8%)	263/911 (28.9%)	0.71 (0.59–0.85)	
60-<90 mL/min/1.73m^2	380/2217 (17.1%)	468/2238 (20.9%)	0.80 (0.70–0.92)	
≥90 mL/min/1.73m^2	128/963 (13.3%)	170/939 (18.1%)	0.70 (0.56–0.89)	
Baseline Triglycerides ≥200 vs <200 mg/dL				0.45
Triglycerides ≥200 mg/dL	430/2481 (17.3%)	559/2469 (22.6%)	0.73 (0.64–0.83)	
Triglycerides <200 mg/dL	275/1605 (17.1%)	342/1620 (21.1%)	0.79 (0.67–0.93)	
Baseline Triglycerides ≥150 vs <150 mg/dL				0.83
Triglycerides ≥150 mg/dL	640/3674 (17.4%)	811/3660 (22.2%)	0.75 (0.68–0.83)	
Triglycerides <150 mg/dL	65/412 (15.8%)	90/429 (21.0%)	0.79 (0.57–1.09)	
Baseline Triglycerides ≥200 and HDL-C ≤35 mg/dL				0.04
Yes	149/823 (18.1%)	214/794 (27.0%)	0.62 (0.51–0.77)	
No	554/3258 (17.0%)	687/3293 (20.9%)	0.79 (0.71–0.88)	
Baseline Statin Intensity				0.12
High	232/1290 (18.0%)	310/1226 (25.3%)	0.69 (0.58–0.82)	
Moderate	424/2533 (16.7%)	543/2575 (21.1%)	0.76 (0.67–0.86)	
Low	48/254 (18.9%)	45/267 (16.9%)	1.12 (0.74–1.69)	
Baseline LDL-C (Derived) by Tertiles				0.62
≤67 mg/dL	244/1481 (16.5%)	302/1386 (21.8%)	0.72 (0.61–0.85)	
>67-≤84 mg/dL	248/1347 (18.4%)	307/1364 (22.5%)	0.81 (0.68–0.96)	
>84 mg/dL	213/1258 (16.9%)	292/1339 (21.8%)	0.74 (0.62–0.89)	
Baseline hsCRP ≤2 vs >2 mg/L				0.07
≤2 mg/L	288/1919 (15.0%)	407/1942 (21.0%)	0.68 (0.58–0.79)	
>2 mg/L	417/2167 (19.2%)	494/2147 (23.0%)	0.81 (0.71–0.93)	

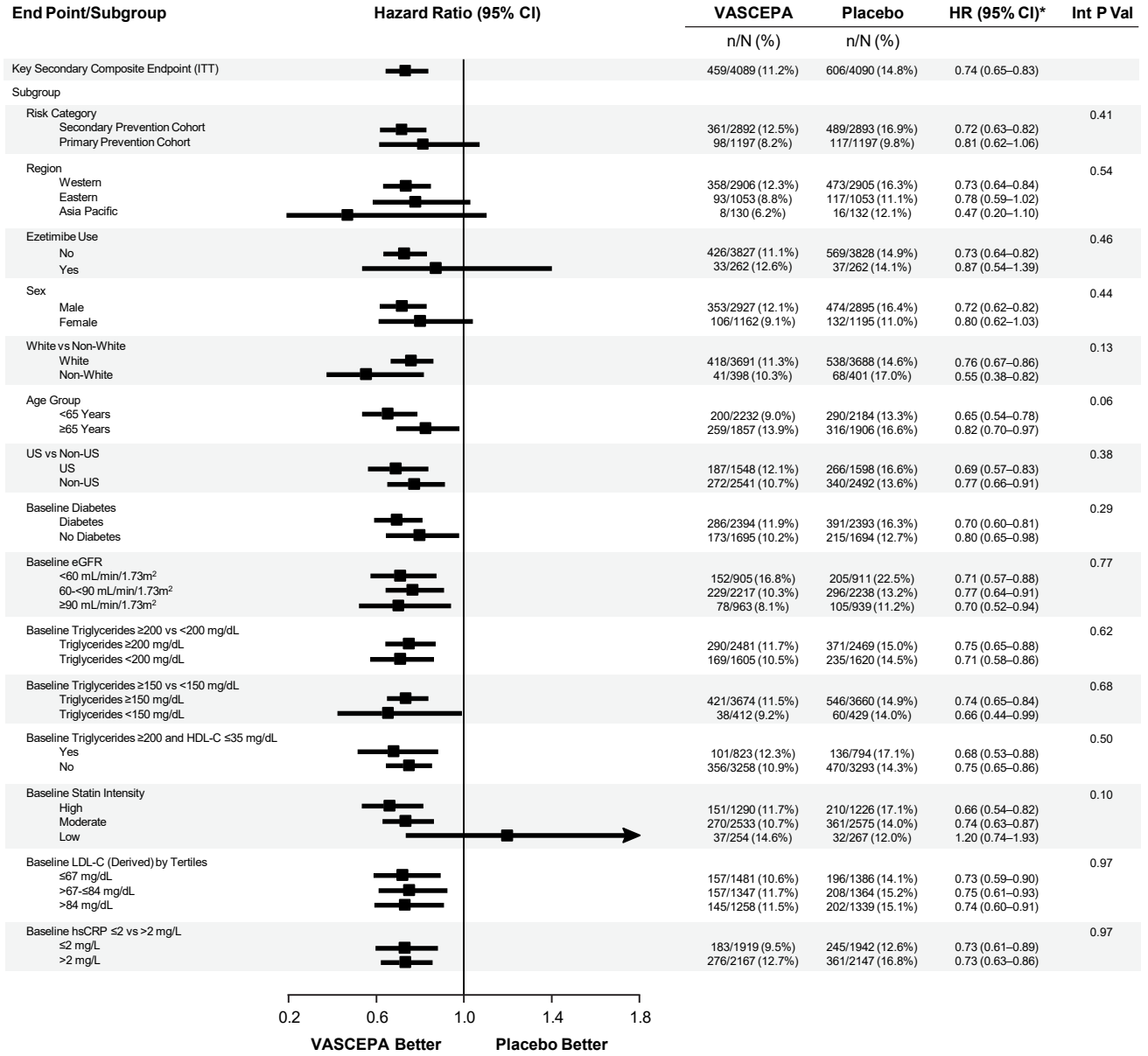
Left of center (1.0) on Hazard Ratio forest plot is better for Vascepa-arm versus placebo-arm

REDUCE-IT results consistently positive except where sample size was very low and statistically not significant

P value $\leq$ 0.15 is statistically significant; many subgroups demonstrated statistical significance reflecting the consistency of the results, despite the study only being powered to detect a 15% RRR in the primary endpoint

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

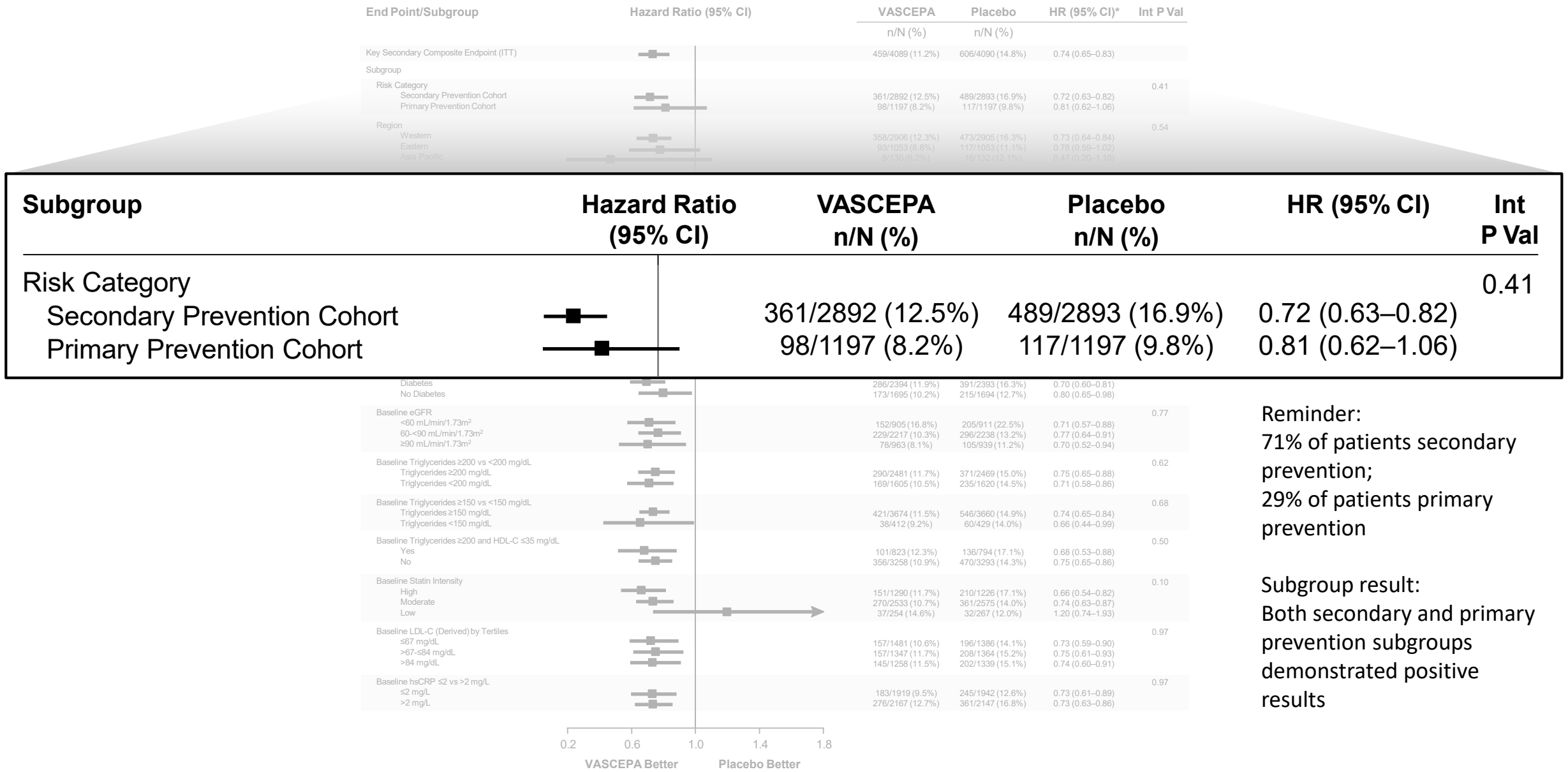
Key Secondary End Point in Subgroups



Similar to primary endpoint, subgroups results for key secondary endpoints (3-Point MACE) were consistently positive further reflecting the robustness of REDUCE-IT results

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Key Secondary End Point in Subgroups



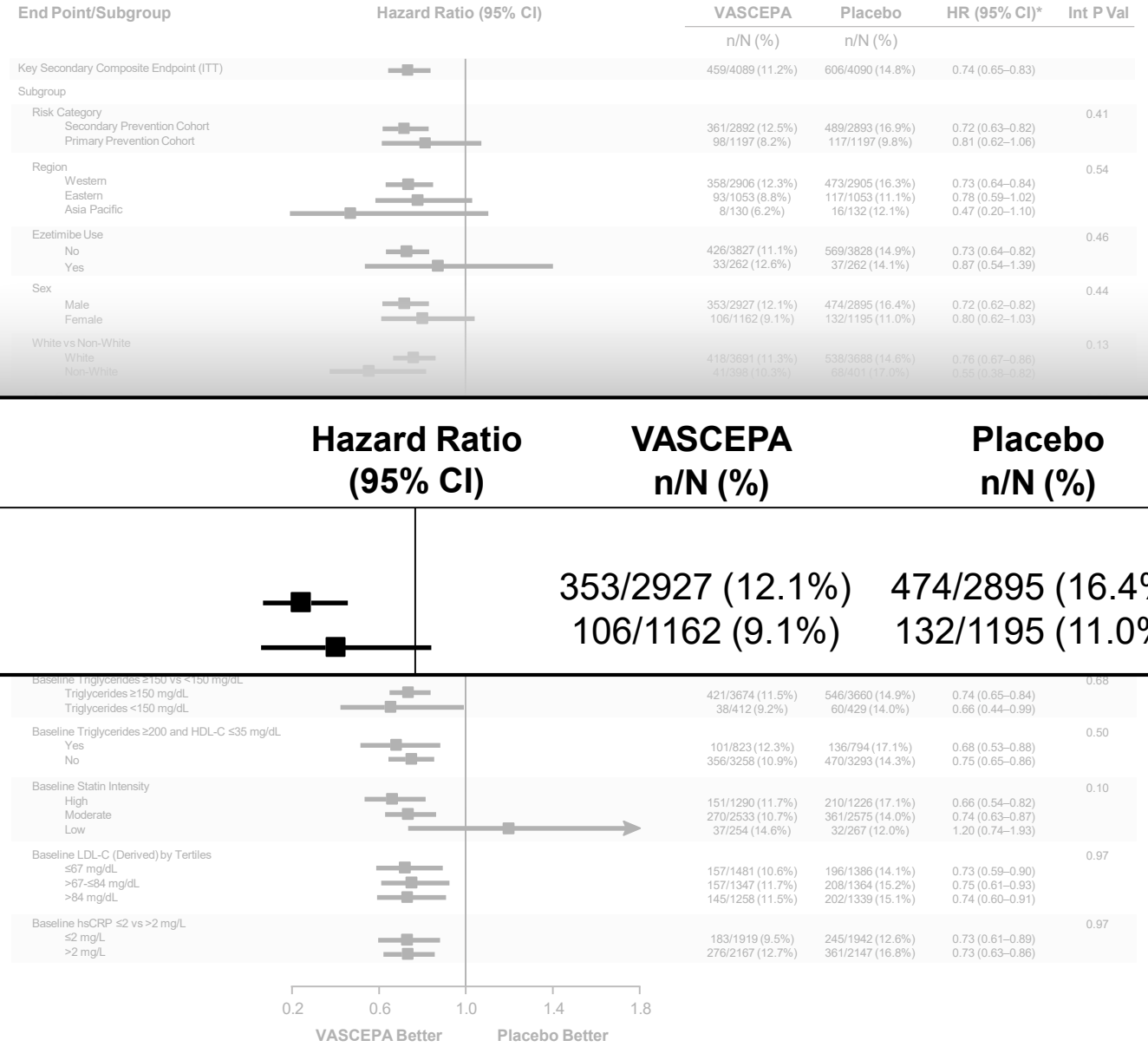
Subgroup	Hazard Ratio (95% CI)	VASCEPA n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Risk Category					0.41
Secondary Prevention Cohort		361/2892 (12.5%)	489/2893 (16.9%)	0.72 (0.63–0.82)	
Primary Prevention Cohort		98/1197 (8.2%)	117/1197 (9.8%)	0.81 (0.62–1.06)	

Reminder:
71% of patients secondary prevention;
29% of patients primary prevention

Subgroup result:
Both secondary and primary prevention subgroups demonstrated positive results

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Key Secondary End Point in Subgroups



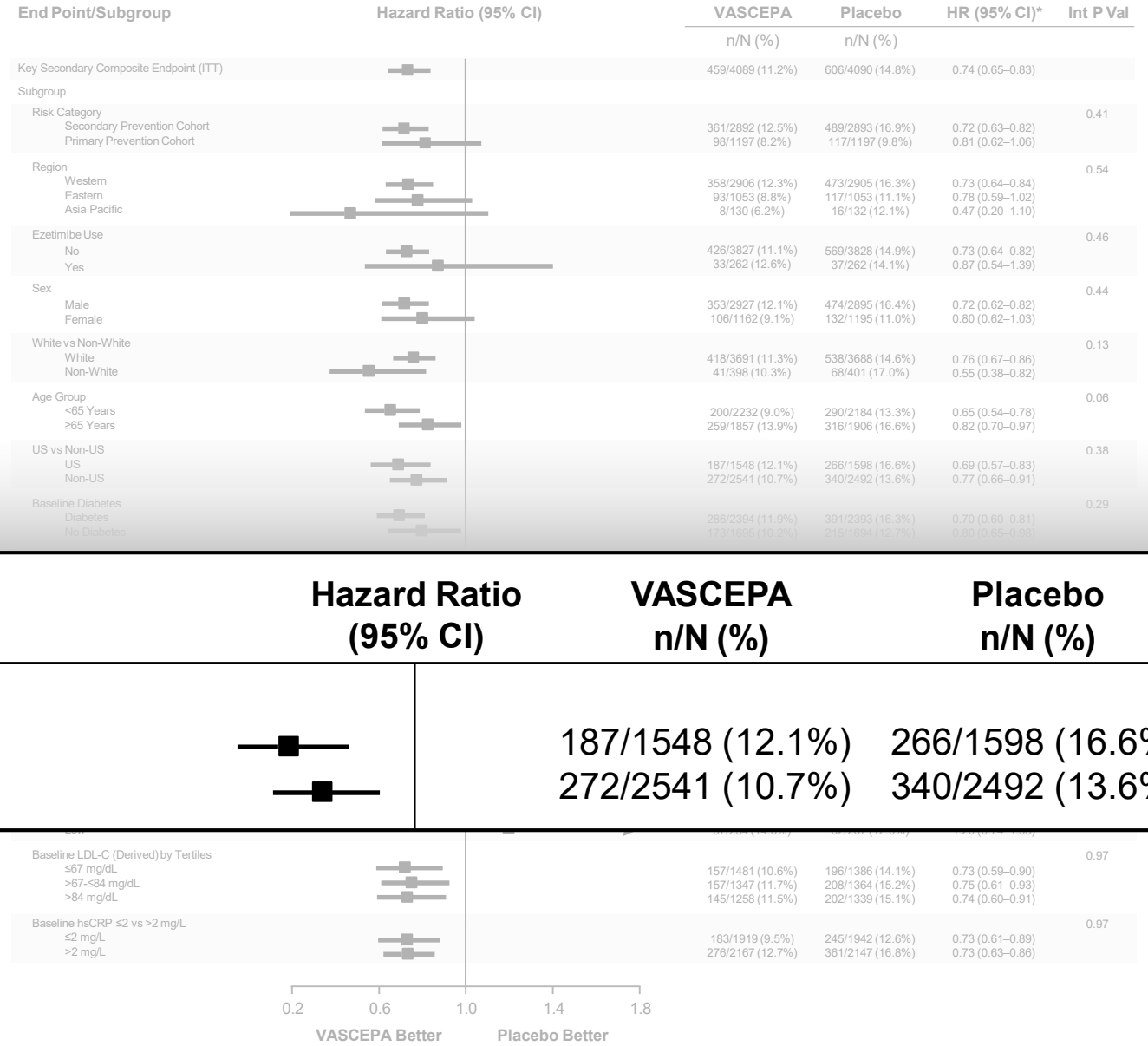
Subgroup	Hazard Ratio (95% CI)	VASCEPA n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Sex					0.44
Male		353/2927 (12.1%)	474/2895 (16.4%)	0.72 (0.62–0.82)	
Female		106/1162 (9.1%)	132/1195 (11.0%)	0.80 (0.62–1.03)	

Vascepa did not discriminate based on sex; benefit observed in both men and women

Most CVOT's have small cohorts of women; in REDUCE-IT women were well-represented

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Key Secondary End Point in Subgroups



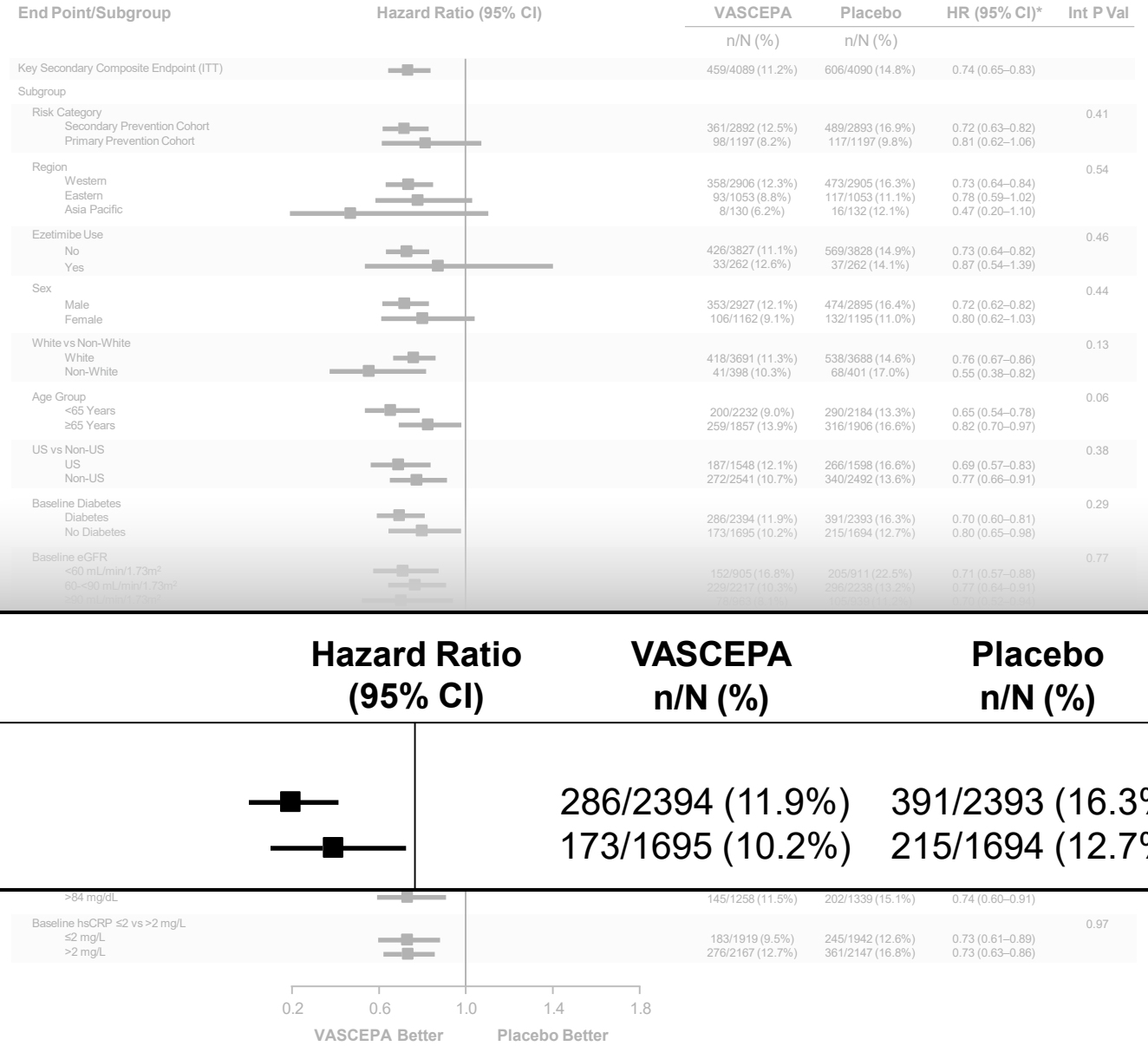
Subgroup	Hazard Ratio (95% CI)	VASCEPA n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
US vs Non-US					0.38
US		187/1548 (12.1%)	266/1598 (16.6%)	0.69 (0.57–0.83)	
Non-US		272/2541 (10.7%)	340/2492 (13.6%)	0.77 (0.66–0.91)	

U.S. cohort of patients was large and Vascepa demonstrated robust results in U.S. patients

Conversion: HR 0.69 is a RRR of 31%

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Key Secondary End Point in Subgroups



Subgroup	Hazard Ratio (95% CI)	VASCEPA n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Diabetes					0.29
Diabetes		286/2394 (11.9%)	391/2393 (16.3%)	0.70 (0.60–0.81)	
No Diabetes		173/1695 (10.2%)	215/1694 (12.7%)	0.80 (0.65–0.98)	

Reminder: 58% of REDUCE-IT patients had diabetes (29% primary prevention patients with diabetes and 29% secondary prevention patients with diabetes)

Risk reduction was robust and consistent across both subgroups

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Key Secondary End Point in Subgroups

Results were independent of baseline TG levels; robust risk reduction observed across TG levels above and below 200 mg/dL

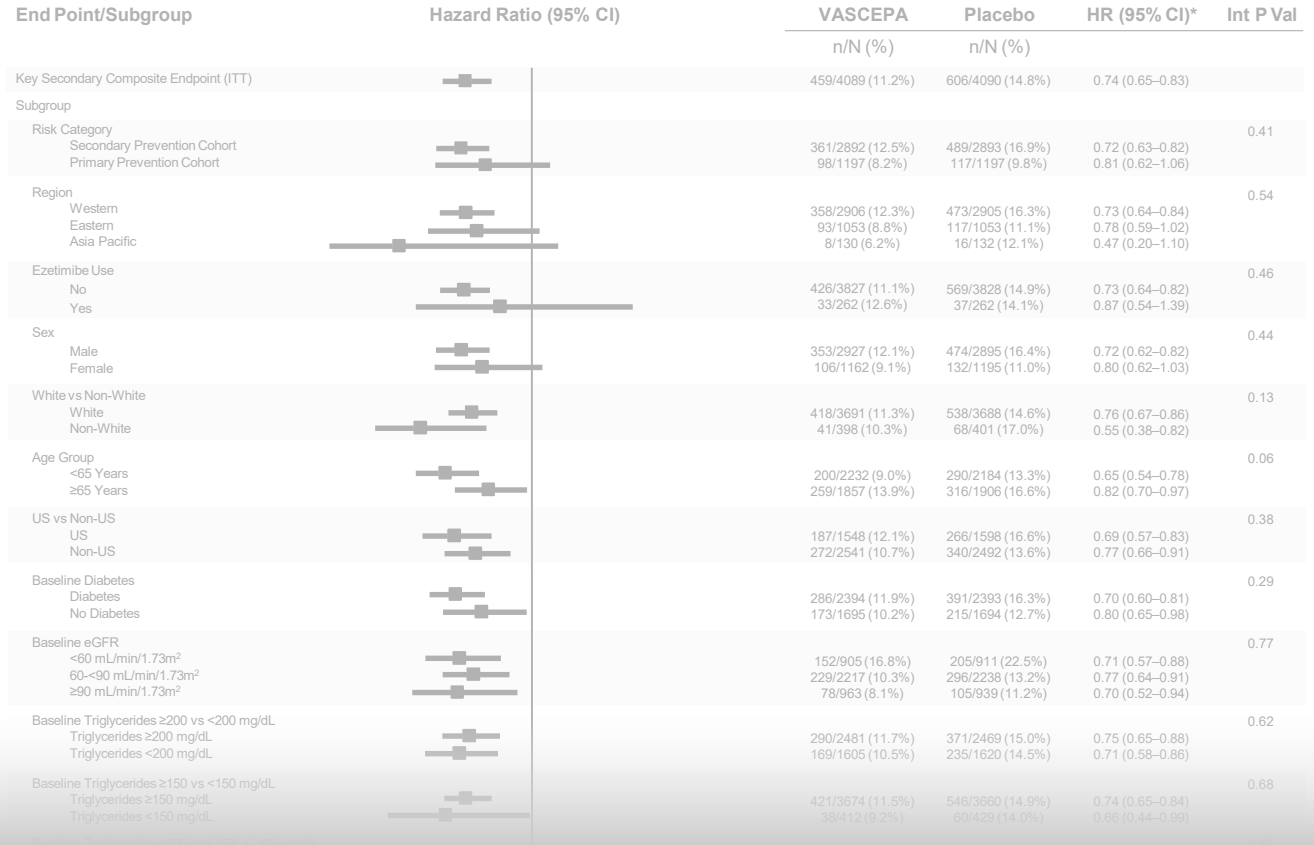
Subgroup	Hazard Ratio (95% CI)	VASCEPA n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Triglycerides ≥200 vs <200 mg/dL					0.62
Triglycerides ≥200 mg/dL		290/2481 (11.7%)	371/2469 (15.0%)	0.75 (0.65–0.88)	
Triglycerides <200 mg/dL		169/1605 (10.5%)	235/1620 (14.5%)	0.71 (0.58–0.86)	

0.2 0.6 1.0 1.4 1.8

VASCEPA Better Placebo Better

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Key Secondary End Point in Subgroups



Robust risk reduction observed across TG levels above and below 150 mg/dL

Reminder: enrollment required TG ≥135 mg/dL

Subgroup	Hazard Ratio (95% CI)	VASCEPA n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Triglycerides ≥150 vs <150 mg/dL					0.68
Triglycerides ≥150 mg/dL		421/3674 (11.5%)	546/3660 (14.9%)	0.74 (0.65–0.84)	
Triglycerides <150 mg/dL		38/412 (9.2%)	60/429 (14.0%)	0.66 (0.44–0.99)	

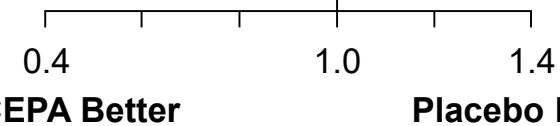
VASCEPA Better Placebo Better

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Prespecified Hierarchical Testing

Primary endpoint was positive, as presented earlier in this presentation and in this forest plot

Endpoint	Hazard Ratio (95% CI)	VASCEPA n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)		705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001



RRR denotes relative risk reduction

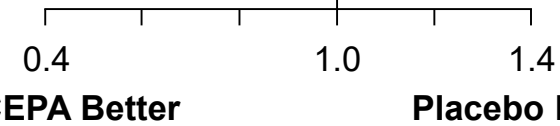
Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018

Prespecified Hierarchical Testing

3-Point MACE key secondary endpoint was positive, as presented earlier in this presentation and in this forest plot

Endpoint	Hazard Ratio (95% CI)	VASCEPA n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)		705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)		459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001



RRR denotes relative risk reduction

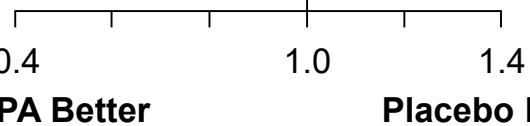
Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018

Prespecified Hierarchical Testing

CV death or MI (heart attack) composite endpoint was positive with **25%** RRR

Endpoint	Hazard Ratio (95% CI)	VASCEPA n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)		705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)		459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction		392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001



RRR denotes relative risk reduction

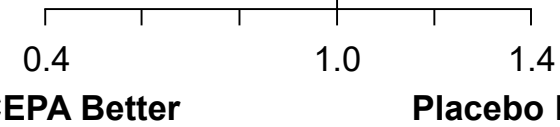
Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018

Prespecified Hierarchical Testing

Heart attack as a standalone endpoint was positive with a **31%** RRR

Endpoint	VASCEPA n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001



RRR denotes relative risk reduction

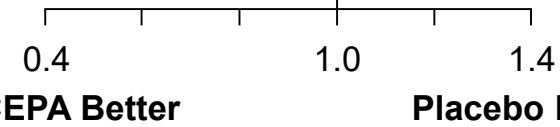
Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018

Prespecified Hierarchical Testing

Urgent or emergent revascularization as a standalone endpoint was positive with a **35%** RRR

Endpoint	Hazard Ratio (95% CI)	VASCEPA n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)		705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)		459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction		392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction		250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization		216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001



RRR denotes relative risk reduction

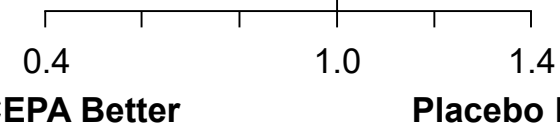
Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018

Prespecified Hierarchical Testing

CV death as a standalone endpoint was positive with a **20%** RRR

Endpoint	VASCEPA n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03



It is infrequent in CVOTs to show a statistically significant benefit in CV death

RRR denotes relative risk reduction

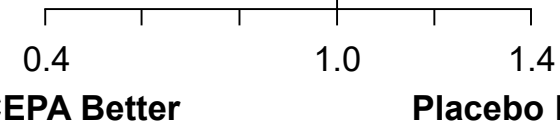
Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018

Prespecified Hierarchical Testing

Hospitalization for unstable angina as a standalone endpoint was positive with a **32%** RRR

Endpoint	VASCEPA n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002



RRR denotes relative risk reduction

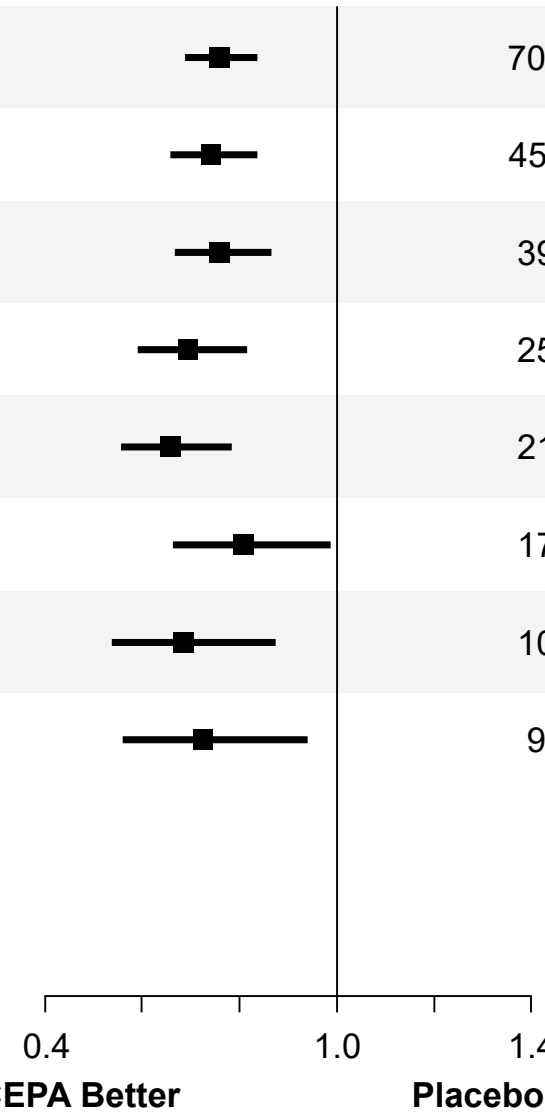
Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018

Prespecified Hierarchical Testing

Stroke as a standalone endpoint was positive with a **28%** RRR

Endpoint	VASCEPA n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01



RRR denotes relative risk reduction

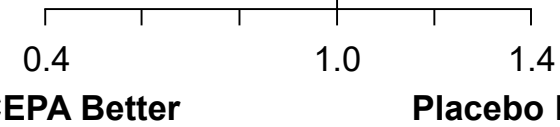
Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018

Prespecified Hierarchical Testing

Composite endpoint of all cause death, heart attack & stroke was positive with a **23%** RRR

Endpoint	VASCEPA n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001



RRR denotes relative risk reduction

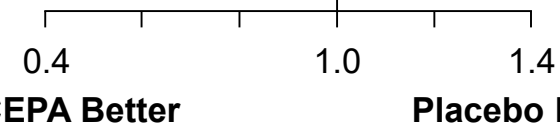
Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018

Prespecified Hierarchical Testing

Top 8 prespecified hierarchy of endpoints all robustly positive and statistically significant

Endpoint	VASCEPA n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001



RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018

Prespecified Hierarchical Testing

All cause death, including death from non-CV causes, as standalone endpoint suggested a **13%** RRR that trended toward, but did not reach, statistical significance

Endpoint	VASCEPA n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
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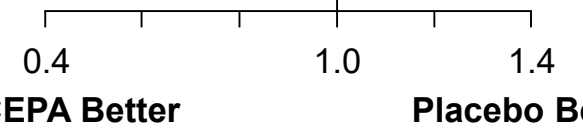
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09



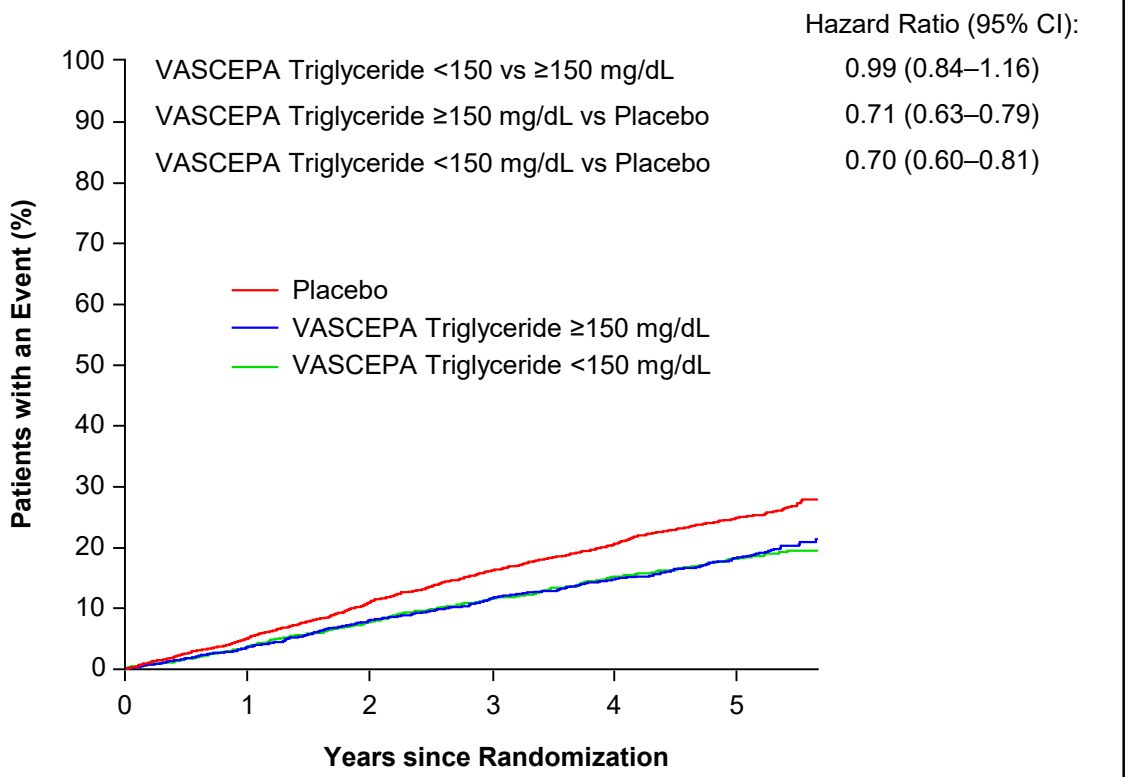
RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

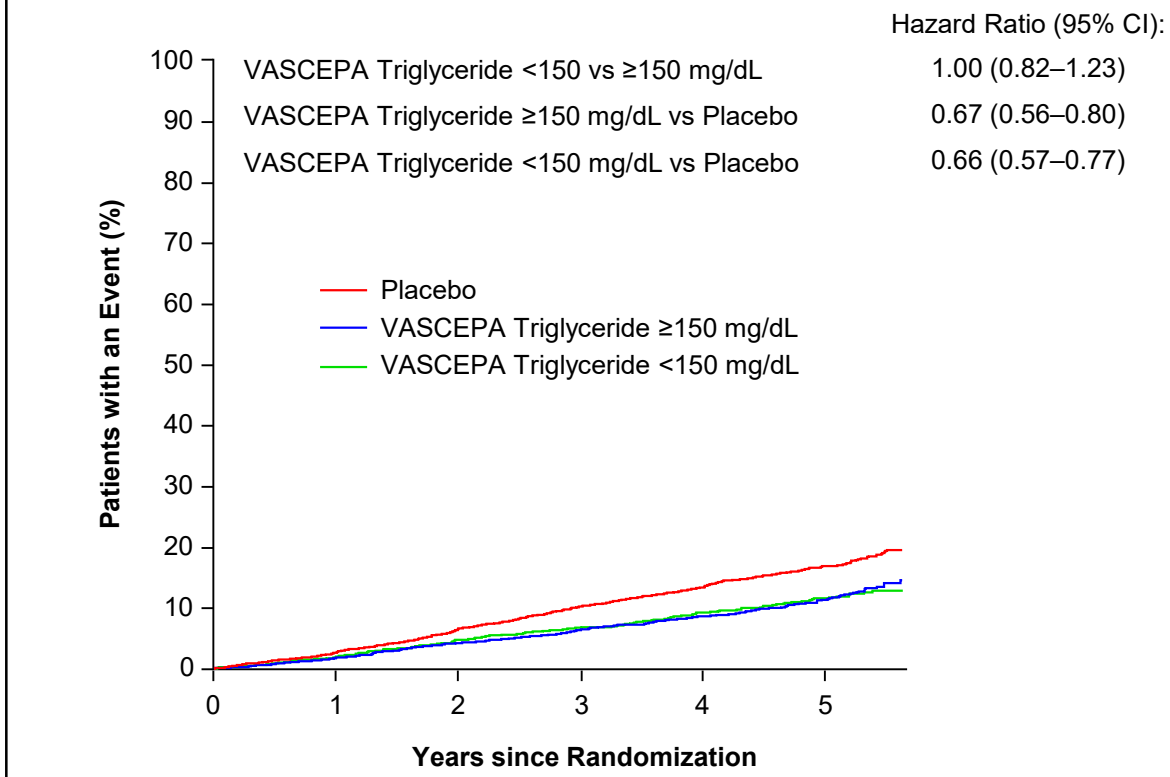
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018

Achieved Triglyceride Levels: <150 mg/dL and ≥150 mg/dL

A Primary End Point by Achieved Triglyceride Level at 1 Year



B Key Secondary End Point by Achieved Triglyceride Level at 1 Year

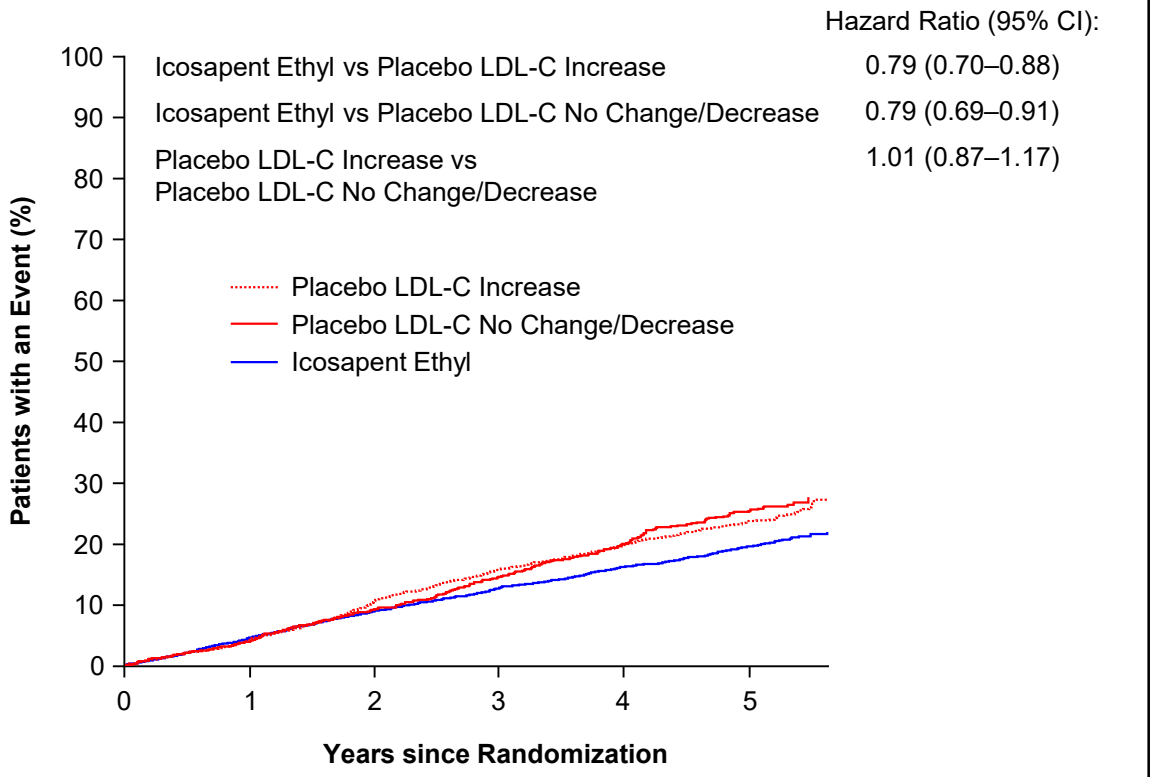


Overlaid blue and green lines reflect that results were similar for Vascepa patients who achieved TG levels < and ≤ 150 mg/dL

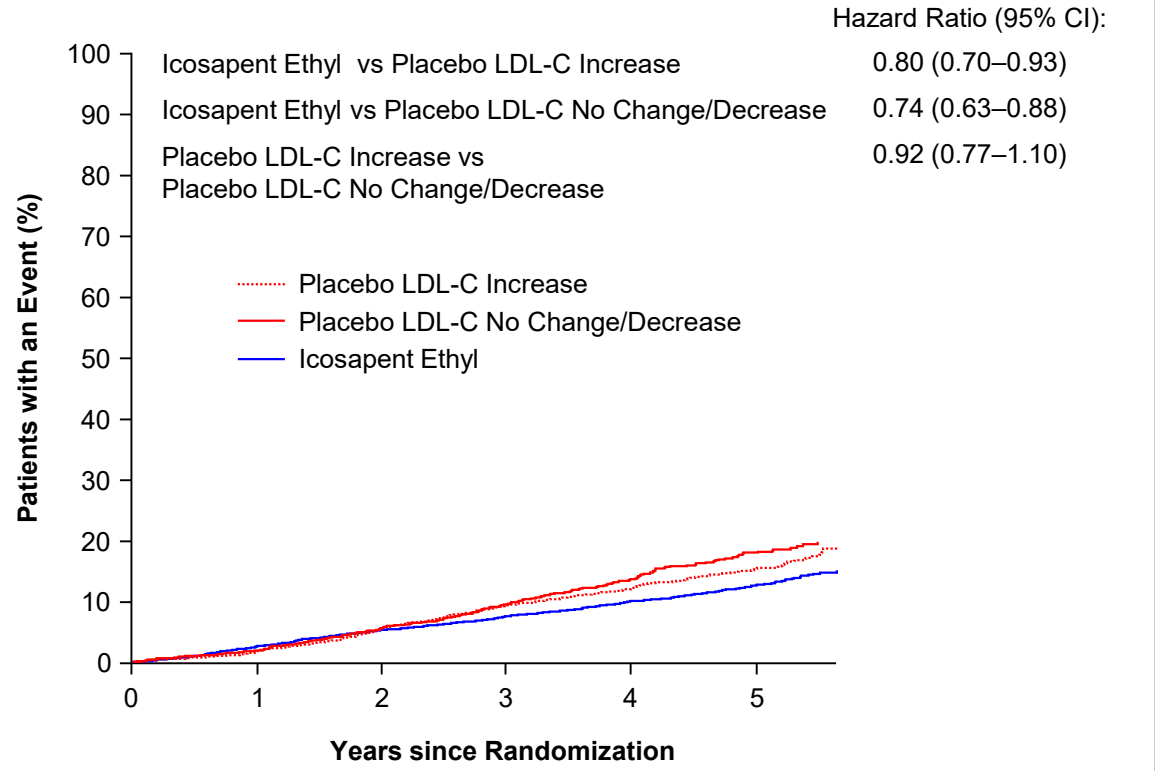
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Primary and Key Secondary End Point in Placebo by Change in LDL-C at 1 Year vs Icosapent Ethyl

A Primary End Point in Placebo by Change in LDL-C at 1 Year vs Icosapent Ethyl



B Key Secondary End Point in Placebo by Change in LDL-C at 1 Year vs Icosapent Ethyl



Overlaid orange and red lines reflect that there were no differences in outcomes for placebo patients with an increase in LDL-C

Data supporting statement in Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Treatment-Emergent Adverse Events

reduce-it

	VASCEPA (N=4089)	Placebo (N=4090)	P-value
Subjects with at Least One TEAE, n (%)	3343 (81.8%)	3326 (81.3%)	0.63
Serious TEAE	1252 (30.6%)	1254 (30.7%)	0.98
TEAE Leading to Withdrawal of Study Drug	321 (7.9%)	335 (8.2%)	0.60
Serious TEAE Leading to Withdrawal of Study Drug	88 (2.2%)	88 (2.2%)	1.00
Serious TEAE Leading to Death	94 (2.3%)	102 (2.5%)	0.61

- Overall event rates were similar across treatment groups
- Adverse and serious adverse events leading to study drug discontinuation were similar across treatment groups
- High adverse event rates reflect at-risk nature of patients and their need for medical care; many adverse events likely not drug related
- Only serious AE >2% was pneumonia (2.6% Vascepa-arm vs 2.9% placebo-arm; p=0.42)
- Safety was reviewed throughout the study by independent Data and Safety Monitoring Committee

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Treatment-Emergent Adverse Event of Interest: Serious Bleeding

	VASCEPA (N=4089)	Placebo (N=4090)	P-value
Bleeding related disorders	111 (2.7%)	85 (2.1%)	0.06
Gastrointestinal bleeding	62 (1.5%)	47 (1.1%)	0.15
Central nervous system bleeding	14 (0.3%)	10 (0.2%)	0.42
Other bleeding	41 (1.0%)	30 (0.7%)	0.19

- Numerically higher AEs relating to bleeding in the Vascepa group, but overall rates were low and the difference did not reach statistical significance
- No fatal bleeding events in either group
- No difference in the adjudicated endpoint of hemorrhagic stroke across treatment groups (13 Vasepa versus 10 placebo; P=0.55)
- No significant CNS bleeding; no significant GI bleeding
- Adjudicated hemorrhagic stroke - no significant difference between treatments
  (13 VASCEPA versus 10 placebo; P=0.55)

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Most Frequent Treatment-Emergent Adverse Events: ≥5% in Either Treatment Group and Significantly Different

Preferred Term	VASCEPA (N=4089)	Placebo (N=4090)	P-value
Diarrhea	367 (9.0%)	453 (11.1%)	0.002
Peripheral edema	267 (6.5%)	203 (5.0%)	0.002
Constipation	221 (5.4%)	149 (3.6%)	<0.001
Atrial fibrillation	215 (5.3%)	159 (3.9%)	0.003
Anemia	191 (4.7%)	236 (5.8%)	0.03

* TEAEs presented above; in addition, the adjudicated endpoint of atrial fibrillation or flutter requiring hospitalization occurred in 3.1% of the Vascepa group versus 2.1% of the placebo group (p=0.004)

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Limitations

Few patients on ezetimibe

- Though data appeared consistent in that subgroup

Concomitant PCSK9 inhibitors prohibited

- Though no reason to think they are not additive

Small difference (5 mg/dL) in LDL-C between groups

- Cannot tell from this study if due to drug or placebo
- Would not account for 25% RRR
- JELIS saw 19% RRR in open label design, no placebo
- Consistent benefit in patients with LDL-C ↑ vs no LDL-C ↑

Pending Questions (not focus of this study)

reduce-it

Cannot comment on mechanisms of benefit from this study

- Consistent reduction across triglyceride range (135-500)
- Similar benefit by 1-year triglycerides < or > 150 mg/dL
- Detailed biomarker and genetic analyses are planned

Cannot comment on cost-effectiveness

- Though with NNT of 21, likely cost-effective
- Formal cost-effectiveness analyses planned
- Full benefits not captured with only first events, await recurrent and total events analyses

Conclusions

Compared with placebo, VASCEPA 4g/day significantly reduced important CV events by **25%**, including:

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Low rate of adverse effects, including:

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- Small but significant increase in atrial fibrillation/flutter

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- Including baseline triglycerides from **135-500** mg/dL

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- Non-statistically significant increase in serious bleeding

Consistent efficacy across multiple subgroups

- Including baseline triglycerides from 135-500 mg/dL
- Including secondary and primary prevention cohorts

We thank the investigators, the study coordinators, and especially the 8,179 patients in REDUCE-IT!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

Article available at https://www.nejm.org
Slides available for download at https://professional.heart.org
or at https://www.ACC.org

End of Detailed Scientific Presentation

- Scientific presentation concluded
- Added perspective provided below

25% RRR on Top of Controlled LDL-C is Landmark Result

Class	CVOT	Relative Risk Reduction (RRR)	Positive CVOT	Peak Net Sales in U.S.
STATIN THERAPY				
Statins	Various	**25-35%**	√	>$20B - 2016
OTHER LDL-CHOLESTEROL LOWERING DRUGS ON TOP OF STATIN THERAPY				
Cholesterol Absorption Inhibitors	IMPROVE-IT	6%	√	$1.8B - 2007
PCSK9 Inhibitors	FOURIER ODYSSEY	15% 15%	√	Recently Launched
OTHER DRUGS ON TOP OF STATIN THERAPY				
Anti-Inflammatory	CANTOS	15%	√	N/A
Omega-3 Mixture (Lovaza 1g/d)	ASCEND/VITAL	Not Significant	X	$1.0B - 2013
EPA (Epadel)	JELIS	19%	√	N/A (in Japan only)
EPA (Vascepa)	**REDUCE-IT**	**25%**	√	TBD

25% RRR with Vascepa is highest of any therapy on top of statins
Many other therapies failed trying to lower CV risk (e.g. CETP inhibitors, fibrates, niacin)
Lipitor (atorvastatin) lowers CV risk ~25%; REDUCE-IT effect is incremental to statins

Added Perspective and Points of Emphasis

Number needed to treat (NNT): 21

- Low NNT combined with affordable price of Vascepa should support continued broad managed care coverage
- For context, NNTs for other notable, but not competitive with Vascepa, drugs:
  - Atorvastatin (Lipitor®)[1]: 45
  - Evolucumab (Repatha®)[2]: 67
    - No head-to-head study with these drugs
    - Study periods and study populations differ

Patients with elevated TG levels have high levels of medical events

- High event rates were supported by real world evidence studies presented in the past year with data from Optum and Kaiser
- Patients need medical attention and proven therapy
- Results in REDUCE-IT were independent of TG level; at 1 year ~36% of patients had TG <150 mg/dL with results similar to patients with TG ≥150 mg/dL

REDUCE-IT was a clinical outcomes study not a TG lowering trial

Clinical effect of Vascepa cannot be generalized to any other product

- This was further evidenced today by VITAL study results and multiple published analysis of other drugs and dietary supplements

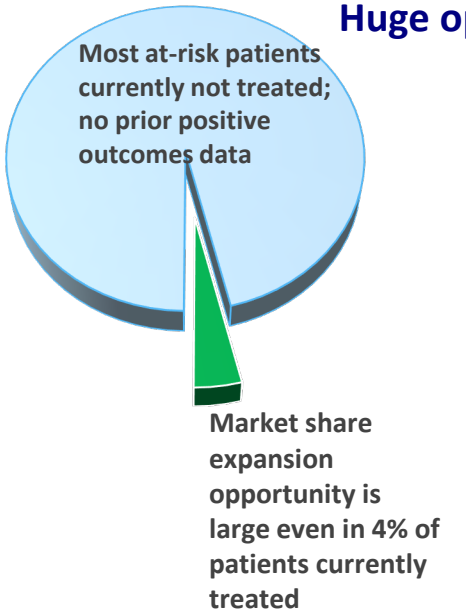
Vascepa Positioned to Potentially Become New Standard of Care for Treatment of CV Risk Beyond Cholesterol Management

Population which could potentially benefit from Vascepa is large

- >25% of adults in U.S. have CV risk factors beyond LDL-C (e.g. ~50M to 70M adults in U.S. alone have elevated triglycerides levels ≥150 mg/dL)
  - Many of these patients are already on statin therapy

Opportunity to grow market and expand market share

Expanding treatment: <4% of patients with elevated triglycerides and other CV risks receive lipid-modifying prescription medication beyond LDL-C therapies



Huge opportunity to address >96% of need; positive outcomes data previously lacking

Expanding market share: the <4% of patients currently prescribed lipid-modifying therapy (excluding LDL-C therapies)

- **Much room to grow**: Vascepa market share H1'18 was ~5% of the <4% Rx use
- **Current competition all have failed CV outcomes studies on top of statins**
  - Earlier generation therapies most widely used to manage lipid levels beyond LDL-C are fenofibrates (Trilipix®, Tricor®), omega-3 mixtures (Lovaza®) and nicotinic acid (Niacin®, Niaspan®)

Amarin's Current Priorities

Regulatory/Medical:

- **Pursue sNDA** for expanded Vascepa indication
  - REDUCE-IT study conducted under SPA; primary endpoint achieved
  - Assuming ordinary FDA review clock (too early to request acceleration); late'19 approval estimate
- **Expand education on REDUCE-IT results** (e.g. CME programs)
- **Support international expansion** via existing and potential new partners

Commercial Expansion:

- **Leverage positive clinical trial results to address large unmet need in CV care**
- **Build-on established infrastructure**
- **Expand U.S. sales force now**
  - Consider further expansion upon label expansion
- **Expand other U.S. promotional activities**
  - Get NEJM publication to healthcare professionals
- **Further expand supply capacity**

AMARIN

Discussion of Primary REDUCE-IT™ Trial Results as Presented on November 10, 2018 at Scientific Sessions of American Heart Association and Simultaneously Published in *The New England Journal of Medicine* (NEJM)

November 10, 2018

NASDAQ: **AMRN**

Pure EPA
Vascepa®
(icosapent ethyl)

NEJM article available at
nejm.org/doi/full/10.1056/NEJMoa1812792

Disclosures and Affiliations of Physician Speakers

- Michael Miller, MD
  - Cardiologist
  - University of Maryland School of Medicine, Baltimore, MD
  - Advisory Board: Amarin independent Steering Committee member of the REDUCE-IT trial
  - Author of NEJM publication
  - Received speaking honoraria and funding for consulting services from Amarin
- Robert Busch, MD
  - Endocrinologist
  - Albany Medical Center
  - REDUCE-IT Investigator
  - Received speaking honoraria and funding for consulting services from Amarin