Icosapent Ethyl Reduces Ischemic Events in Patients with High Triglycerides and Low High-Density Lipoprotein Cholesterol Levels: REDUCE-IT High TG/Low HDL-C Analyses

Xiaowen Wang, M.D.,[1] Deepak L. Bhatt, M.D., M.P.H.,[1] Michael Miller, M.D.,[2] Ph. Gabriel Steg, M.D.,[3,4] Eliot A. Brinton M.D.,[5] Terry A. Jacobson, M.D.,[6] Steven B. Ketchum, Ph.D.,[7] Rebecca A. Juliano, Ph.D.,[7] Lixia Jiao, Ph.D.,[7] Ralph T. Doyle, Jr., B.A.,[7] Craig Granowitz, M.D., Ph.D.,[7] Christina Copland, Ph.D., M.P.H.[7] Jean-Claude Tardif, M.D.,[8] Christie M. Ballantyne, M.D.,[9] Mathew J. Budoff, M.D.,[10] R. Preston Mason, Ph.D.,[11] William E. Boden, M.D.,[12] on Behalf of the **REDUCE-IT** Investigators

[1] Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, MA; [2] Department of Medicine, University of Maryland School of Medicine, Baltimore, MD; [3] Université de Paris, AP-HP (Assistance Publique-Hôpitaux de Paris), [4] Hôpital Bichat, FACT (French Alliance for Cardiovascular Trials), INSERM U-1148, Paris, France; [5] Utah Lipid Center, Salt Lake City, UT; [6] Office of Health Promotion and Disease Prevention, Department of Medicine, Emory University School of Medicine, Atlanta, GA; [7] Amarin Pharma, Inc. (Amarin), Bedminster, NJ; [8] Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada; [9] Department of Medicine, Baylor College of Medicine; [10] Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Torrance, CA; [11] Elucida Research LLC, Beverly, MA; [12] VA New England Healthcare System, Boston, MA, and Boston University School of Medicine, Boston, MA

Wang X, Bhatt DL, Miller M, et al., ACC 2021 virtual flatboard poster.

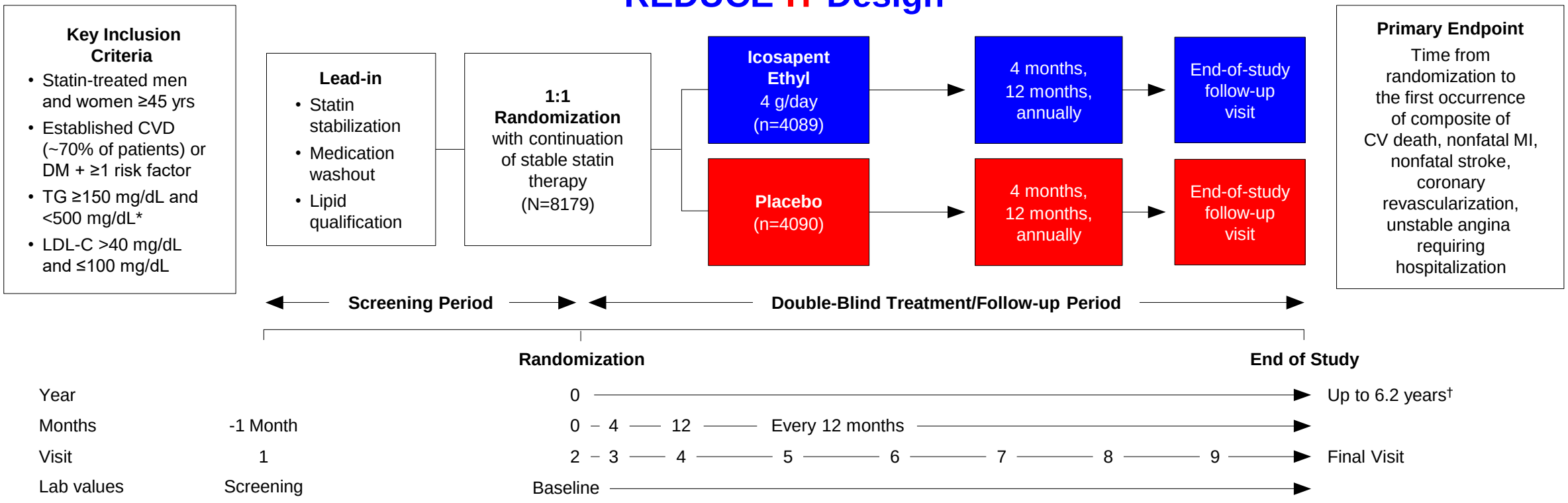
(The presented multi-panel poster [1-page layout has been reformatted verbatim to slide format for ease of visualization.)

BACKGROUND & DESIGN

- **REDUCE-IT**, a multicenter, double-blind, placebo-controlled trial, randomized 8,179 statin-treated patients with established cardiovascular (CV) disease or risk factors, and well-controlled LDL-C (41-100 mg/dL), but elevated triglycerides (TG; 135-499 mg/dL), to IPE 4g daily or placebo; median follow-up was 4.9 years. The primary composite endpoint included CV death, myocardial infarction (MI), stroke, coronary revascularization, and unstable angina; the key secondary composite endpoint included CV death, MI, and stroke.

BACKGROUND & DESIGN

REDUCE-IT Design



*Due to the variability of triglycerides, a 10% allowance existed 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.

†Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

- **REDUCE-IT** demonstrated a 25% relative risk reduction in the primary endpoint. The similarly designed STRENGTH study failed to show benefit of a mixed omega-3 therapy. We evaluated **REDUCE-IT** results per various high TG and low high-density lipoprotein cholesterol (HDL-C) thresholds.

Wang X, Bhatt DL, Miller M, et al., ACC 2021 (virtual)

METHODS

Prespecified and *post hoc* analyses of first and total primary and key secondary endpoint events in **REDUCE-IT** patients with prespecified TG ≥200 and HDL-C ≤35 mg/dL; guideline-informed ≥150 mg/dL and <40/50 mg/dL (men/women); or STRENGTH inclusion criteria ≥180 and <42/47 mg/dL (men/women).

RESULTS

In the full **REDUCE-IT** cohort, icosapent ethyl 4g/day significantly reduced first and total primary and key secondary endpoint events by 25 to 30% compared with placebo.

This robust result was also observed within prespecified dyslipidemia subgroups with icosapent ethyl relative to placebo:

- TG above or below 200 mg/dL experienced similar reductions in primary (RRR 27% & 21%, respectively), key secondary (25% & 29%), total primary (34% and 24%), and total key secondary (29% & 28%) events (all interaction p-values [p_{int}] = ns).
- Patients with or without dyslipidemia defined as TG ≥200 and HDL-C ≤35 mg/dL both had substantial reductions in the primary endpoint, but those with dyslipidemia observed greater reduction (RRR 38% vs 21%, p_{int} = 0.04).
  - However, reductions in the key secondary (RRR 32% & 25%, respectively), total primary (39% & 28%), and total key secondary (37% & 26%) endpoint events were similar regardless of the presence or absence of dyslipidemia (all p_{int} = ns).

Wang X, Bhatt DL, Miller M, et al., ACC 2021 (virtual)

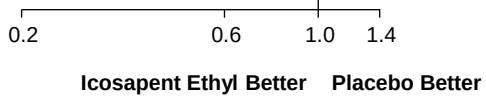
(This slide is the top half of the full chart shown on the poster and has been enlarged for ease of visualization.)

RESULTS (cont.)

Substantial and Consistent Reductions in Total (First and Subsequent) Primary and Key Secondary Endpoint Events Across Various Definitions of Dyslipidemia:

Risk reduction observed regardless of presence or absence of dyslipidemia or degree of dyslipidemia

Endpoint/Subgroup	N	Icosapent Ethyl, Rate per 1000 Pt. Yrs.	Placebo, Rate per 1000 Pt. Yrs.	ARD, Events per 1000 Pt. Yrs.	Rate Ratio (95% CI)	P-value for Int.
Total Events Overall Primary Endpoint	8179	61.1	88.8	-27.8	0.70 (0.62, 0.78)	
Prespecified REDUCE-IT Subgroups						
Baseline triglycerides ≥200 mg/dL						0.26
Yes	4950	63.9	98.9	-35.0	0.66 (0.57, 0.77)	
No	3225	57.2	75.2	-17.9	0.76 (0.63, 0.91)	
Baseline HDL-C ≤35 mg/dL						0.29
Yes	2201	70.1	113.2	-43.1	0.63 (0.52, 0.77)	
No	5956	57.7	80.4	-22.8	0.72 (0.63, 0.83)	
Baseline triglycerides ≥200 and HDL-C ≤35 mg/dL						0.20
Yes	1617	70.1	121.3	-51.2	0.61 (0.48, 0.76)	
No	6551	58.9	81.9	-23.0	0.72 (0.64, 0.82)	
Guideline-informed Subgroups						
Baseline triglycerides ≥150 mg/dL						0.94
Yes	7334	61.7	90.3	-28.6	0.69 (0.62, 0.78)	
No	841	55.9	77.7	-21.9	0.71 (0.49, 1.03)	
Baseline HDL-C <40 (men) or <50 (women) mg/dL						0.43
Yes	5034	60.7	92.9	-32.2	0.68 (0.58, 0.78)	
No	3123	61.4	82.0	-20.5	0.74 (0.62, 0.88)	
Baseline triglycerides ≥150 and HDL-C <40 (men) or <50 (women) mg/dL						0.38
Yes	4641	61.0	95.2	-34.2	0.67 (0.57, 0.78)	
No	3519	60.9	80.7	-19.8	0.74 (0.62, 0.87)	
STRENGTH-informed Subgroups						
Baseline triglycerides ≥180 mg/dL						0.32
Yes	5957	62.3	94.9	-32.6	0.67 (0.59, 0.77)	
No	2218	58.2	74.7	-16.5	0.77 (0.62, 0.96)	
Baseline HDL-C <42 (men) or <47 (women) mg/dL						0.66
Yes	5309	61.5	92.1	-30.6	0.68 (0.59, 0.79)	
No	2848	60.0	82.4	-22.4	0.72 (0.60, 0.88)	
Baseline triglycerides ≥180 HDL-C <42 (men) or <47 (women) mg/dL						0.33
Yes	4109	63.5	99.6	-36.1	0.66 (0.56, 0.77)	
No	4055	58.5	79.0	-20.5	0.74 (0.63, 0.87)	



Wang X, Bhatt DL, Miller M, et al., ACC 2021 (virtual)

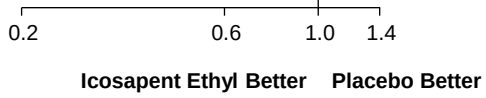
(This slide is the bottom half of the full chart shown on the poster and has been enlarged for ease of visualization.)

RESULTS (cont.)

Substantial and Consistent Reductions in Total (First and Subsequent) Primary and Key Secondary Endpoint Events Across Various Definitions of Dyslipidemia:

Risk reduction observed regardless of presence or absence of dyslipidemia or degree of dyslipidemia (cont.)

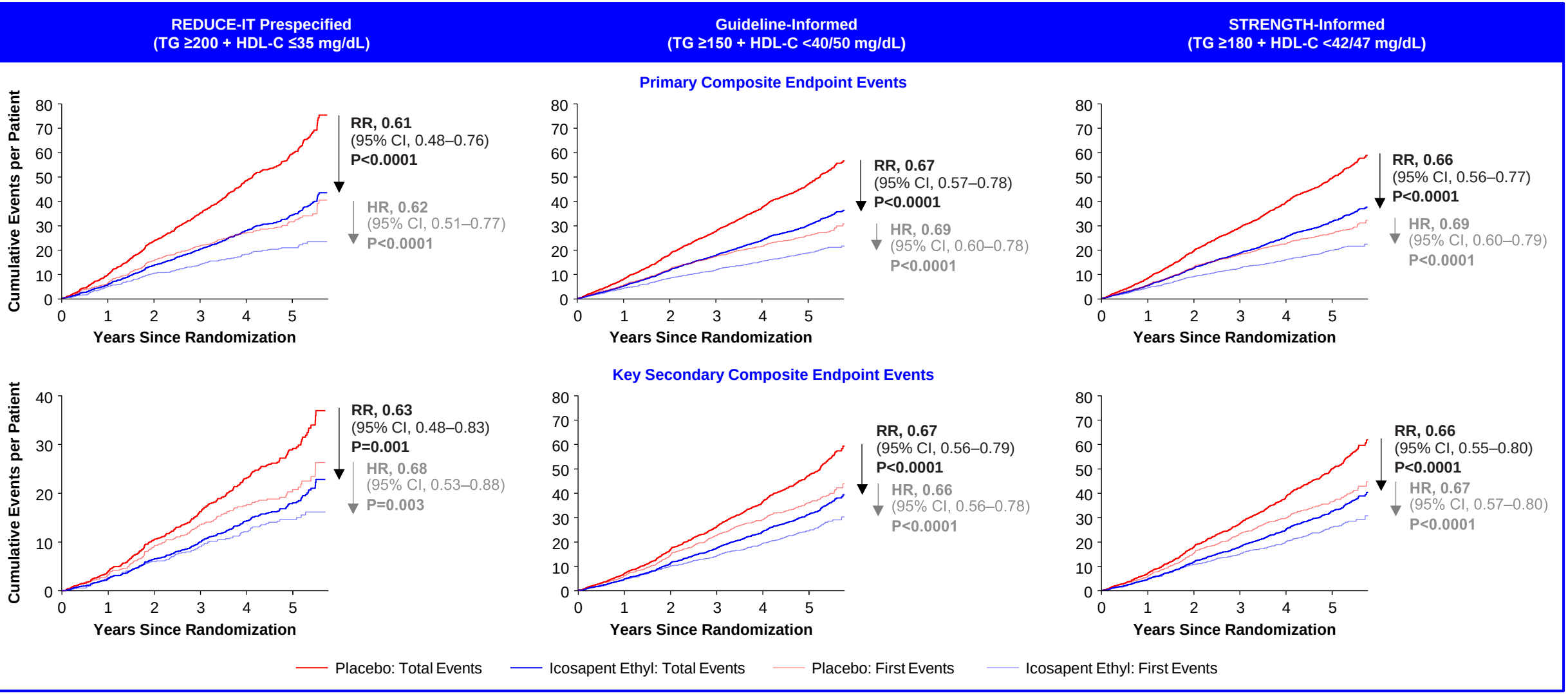
Endpoint/Subgroup	N	Icosapent Ethyl, Rate per 1000 Pt. Yrs.	Placebo, Rate per 1000 Pt. Yrs.	ARD, Events per 1000 Pt. Yrs.	Rate Ratio (95% CI)	P-value for Int.
Total Events Overall Key Secondary	8179	31.7	44.1	-12.4	0.72 (0.63, 0.82)	
Prespecified REDUCE-IT Subgroups						
Baseline triglycerides ≥200 mg/dL						0.89
Yes	4950	33.9	47.7	-13.8	0.71 (0.60, 0.84)	
No	3225	28.6	39.2	-10.6	0.72 (0.58, 0.90)	
Baseline HDL-C ≤35 mg/dL						0.28
Yes	2201	36.1	56.8	-20.7	0.64 (0.51, 0.80)	
No	5956	30.0	39.6	-9.6	0.77 (0.64, 0.88)	
Baseline triglycerides ≥200 and HDL-C ≤35 mg/dL						0.37
Yes	1617	35.9	57.7	-21.8	0.63 (0.48, 0.83)	
No	6551	30.6	41.1	-10.6	0.74 (0.63, 0.86)	
Guideline-informed Subgroups						
Baseline triglycerides ≥150 mg/dL						0.88
Yes	7334	32.4	45.0	-12.6	0.72 (0.62, 0.82)	
No	841	26.1	37.4	-11.2	0.69 (0.44, 1.08)	
Baseline HDL-C <40 (men) or <50 (women) mg/dL						0.20
Yes	5034	31.3	46.7	-15.4	0.67 (0.57, 0.79)	
No	3123	32.0	39.5	-7.5	0.80 (0.65, 0.99)	
Baseline triglycerides ≥150 and HDL-C <40 (men) or <50 (women) mg/dL						0.21
Yes	4641	31.7	47.7	-16.0	0.67 (0.56, 0.79)	
No	3519	31.4	39.1	-7.7	0.79 (0.64, 0.97)	
STRENGTH-informed Subgroups						
Baseline triglycerides ≥180 mg/dL						0.76
Yes	5957	32.9	45.6	-12.7	0.72 (0.62, 0.85)	
No	2218	28.7	40.6	-11.9	0.69 (0.54, 0.90)	
Baseline HDL-C <42 (men) or <47 (women) mg/dL						0.15
Yes	5309	31.3	47.0	-15.7	0.67 (0.57, 0.79)	
No	2848	32.2	38.4	-6.2	0.83 (0.66, 1.03)	
Baseline triglycerides ≥180 HDL-C <42 (men) or <47 (women) mg/dL						0.22
Yes	4109	32.7	50.0	-17.4	0.66 (0.55, 0.80)	
No	4055	30.5	38.5	-8.0	0.78 (0.65, 0.94)	



Wang X, Bhatt DL, Miller M, et al., ACC 2021 (virtual)

RESULTS (cont.)

Substantial and Consistent Reductions in First and Total (First and Subsequent) Primary and Key Secondary Endpoint Events Across Various Definitions of Dyslipidemia:
Similar relative risk reductions of 31-39% across dyslipidemia definitions

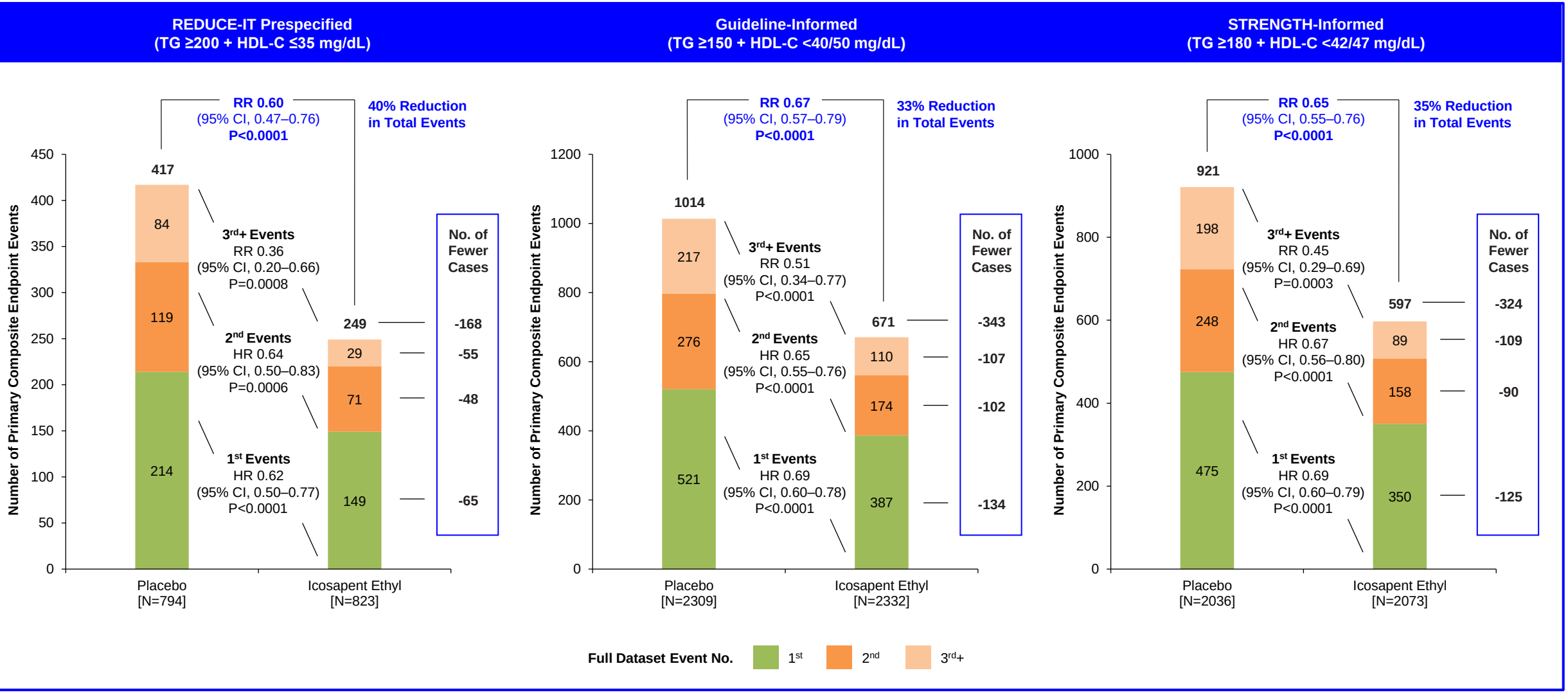


Wang X, Bhatt DL, Miller M, et al., ACC 2021 (virtual)

RESULTS (cont.)

Substantial and Consistent Reductions in First and Subsequent Primary Endpoint Events Across Various Definitions of Dyslipidemia (Full Dataset):

Similar relative risk reductions of 33-40% across dyslipidemia definitions



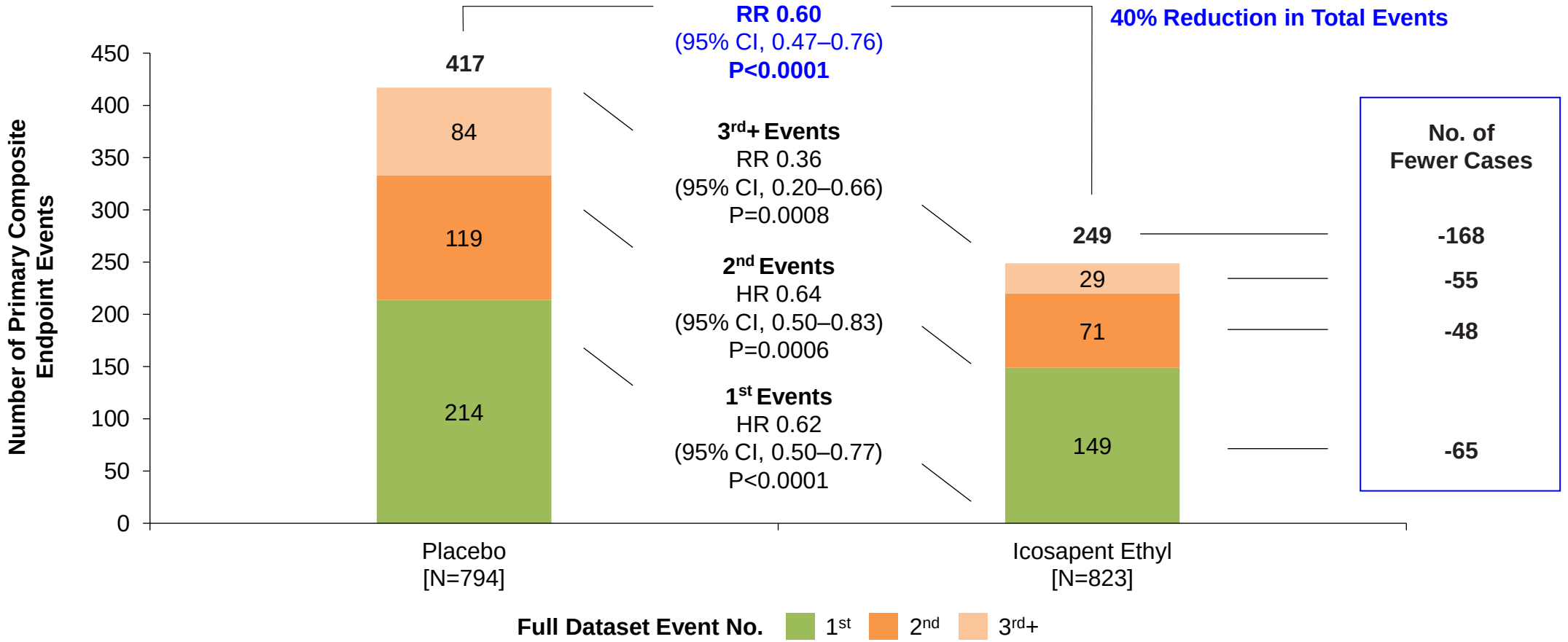
Wang X, Bhatt DL, Miller M, et al., ACC 2021 (virtual)

(This slide shows only the "REDUCE-IT Prespecified" subgroup from slide 9 and has been enlarged for ease of visualization.)

RESULTS (cont.)

Substantial and Consistent Reductions in First and Subsequent Primary Endpoint Events Across Various Definitions of Dyslipidemia (Full Dataset):
Similar relative risk reductions of 33-40% across dyslipidemia definitions

REDUCE-IT Prespecified
(TG ≥200 + HDL-C ≤35 mg/dL)



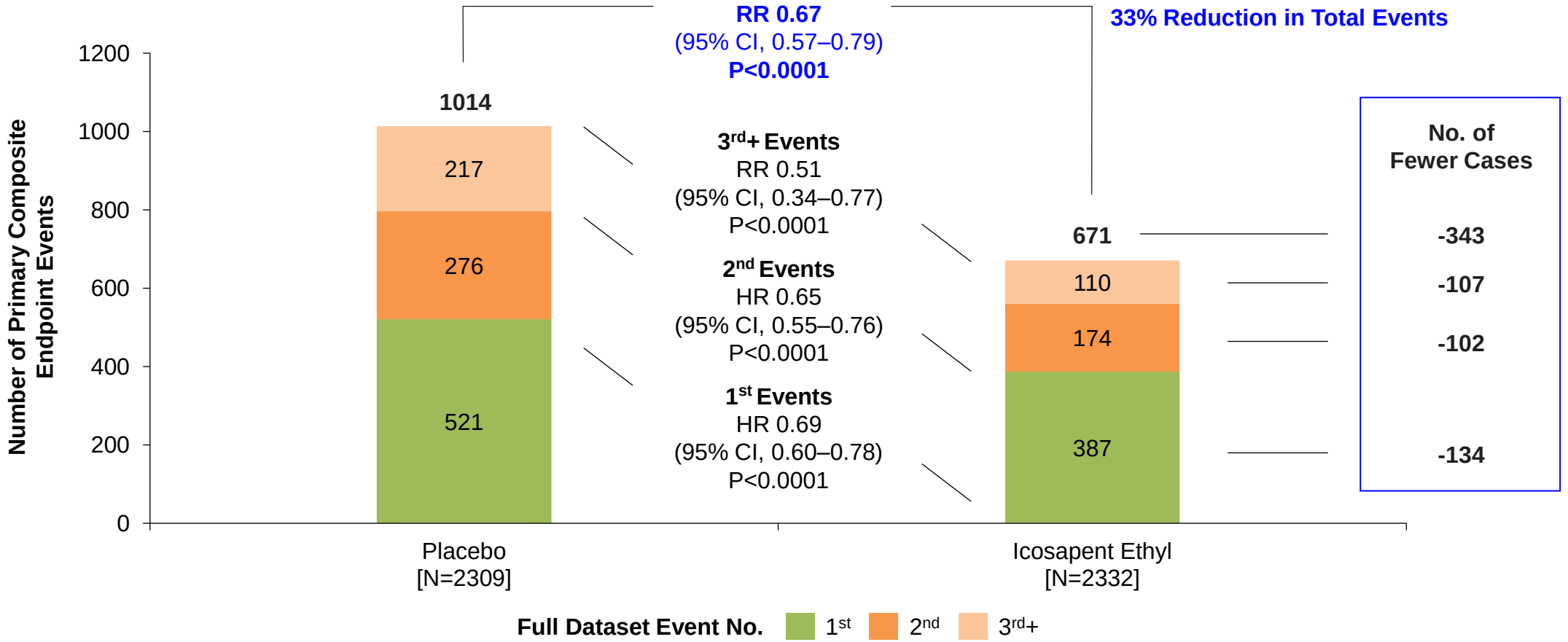
Wang X, Bhatt DL, Miller M, et al., ACC 2021 (virtual)

(This slide shows only the "Guideline-Informed" subgroup from slide 9 and has been enlarged for ease of visualization.)

RESULTS (cont.)

Substantial and Consistent Reductions in First and Subsequent Primary Endpoint Events Across Various Definitions of Dyslipidemia (Full Dataset):
Similar relative risk reductions of 33-40% across dyslipidemia definitions (cont.)

Guideline-Informed
(TG ≥150 + HDL-C <40/50 mg/dL)



Wang X, Bhatt DL, Miller M, et al., ACC 2021 (virtual)

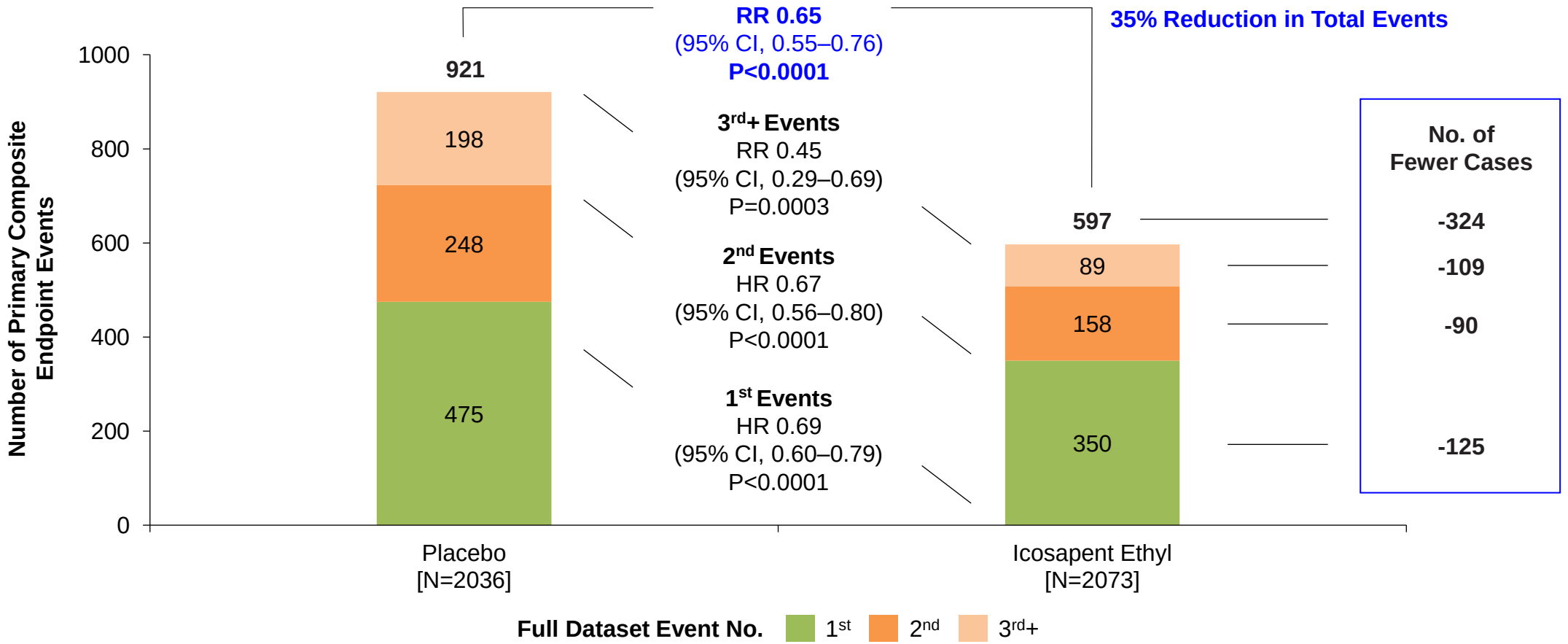
(This slide shows only the "STRENGTH-Informed" subgroup from slide 9 and has been enlarged for ease of visualization.)

RESULTS (cont.)

Substantial and Consistent Reductions in First and Subsequent Primary Endpoint Events Across Various Definitions of Dyslipidemia (Full Dataset):

Similar relative risk reductions of 33-40% across dyslipidemia definitions (cont.)

STRENGTH-Informed
(TG ≥180 + HDL-C <42/47 mg/dL)



Wang X, Bhatt DL, Miller M, et al., ACC 2021 (virtual)

SAFETY

- Adverse events were similar across dyslipidemia subgroups.
- No differences were observed between icosapent ethyl and placebo in overall tolerability or adverse events.
- More bleeding occurred with icosapent ethyl versus placebo, but there were no significant differences in hemorrhagic stroke or fatal bleeding.
- More atrial fibrillation/flutter occurred with icosapent ethyl versus placebo, though ischemic stroke was significantly reduced.

Wang X, Bhatt DL, Miller M, et al., ACC 2021 (virtual)

LIMITATIONS

- These data include both prespecified and *post hoc* analyses.
- **REDUCE-IT** was designed and powered for the primary composite endpoint; it was not powered for subgroup analyses.
- **REDUCE-IT** patients were enrolled with statin-stabilized qualifying TG ≥135 mg/dL, but there were no HDL-C inclusion criteria, and patients were not stratified by any of the prespecified subgroups of TG ≥200 mg/dL, HDL-C ≤35 mg/dL, or the combination of both.

Wang X, Bhatt DL, Miller M, et al., ACC 2021 (virtual)

CONCLUSION

- Event rates were numerically higher with increasing degrees of dyslipidemia.
- Relative risk reductions with icosapent ethyl were similar regardless of the presence or absence of dyslipidemia or the degree of dyslipidemia.
- Icosapent ethyl provides substantial CV risk reduction in both patients with but also in those without elevated TG and/or low HDL-C.
- Compared with placebo**, icosapent ethyl 4g/day significantly reduced first and total primary and key secondary endpoint events by 30% to 40% in patients with dyslipidemia** defined by various high TG plus low HDL-C levels.

Wang X, Bhatt DL, Miller M, et al., ACC 2021 (virtual)

DISCLOSURES

REDUCE-IT was sponsored by Amarin Pharma, Inc.

Dr. Wang has no disclosures. Dr. Bhatt served as the principal investigator for **REDUCE-IT** and his institution received research funding from Amarin. This presentation may include off-label and/or investigational uses of drugs.

REFERENCES

1. Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019;380:11-22. Bhatt DL. AHA 2018, Chicago.

2. Bhatt DL, Steg PG, Miller M, et al. J Am Coll Cardiol. 2019;73:2791-2802. Bhatt DL. ACC 2019, New Orleans.