Reduction in Heart Failure with Icosapent Ethyl: Insights from REDUCE-IT HF

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(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 4 g 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.

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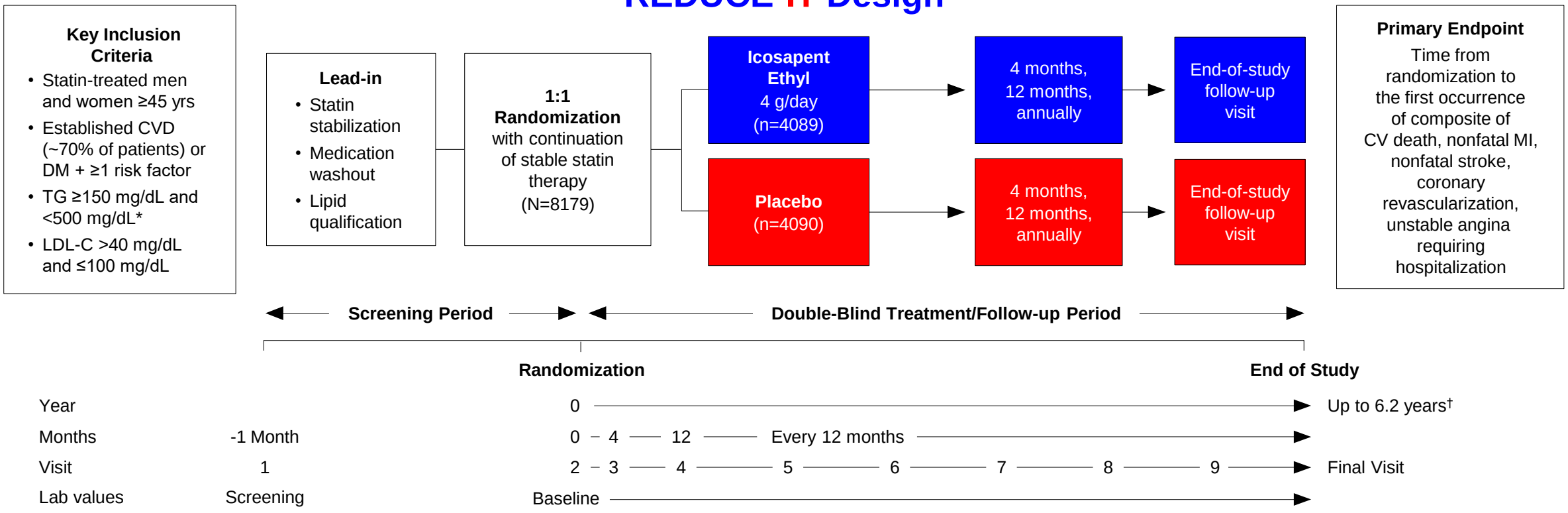
BACKGROUND & DESIGN

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, and a 26% relative risk reduction in the key secondary endpoint.

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METHODS

We evaluated the effects of icosapent ethyl on heart failure by achieved estimated serum eicosapentaenoic acid (EPA) levels in **REDUCE-IT**. New heart failure and new heart failure requiring hospitalization were prespecified tertiary endpoints. *Post hoc* analyses were conducted based on average estimated on-treatment EPA levels in patients in the icosapent ethyl group with available EPA measurements, as compared to patients in the placebo group with available EPA measurements.

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RESULTS

- In the full REDUCE-IT cohort, icosapent ethyl 4 g/day significantly reduced first and total primary and key secondary endpoint events by 25 to 30% compared with placebo.
- Prespecified tertiary endpoints of new heart failure (HR=0.95; 95% CI 0.77, 1.17; p=0.63) and new heart failure requiring hospitalization (HR=0.97; 95% CI 0.77, 1.22; p=0.78) were not significant.
- Analyses by estimated on-treatment EPA levels in the icosapent ethyl group suggest potential benefit in new heart failure with higher achieved EPA levels.

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RESULTS (cont.)

REDUCE-IT Baseline Demographics by Icosapent Ethyl Estimated Average On-treatment EPA or Placebo

	Icosapent Ethyl Estimated Average EPA (µg/mL)			
	≤100 (N=970)	>100 to ≤150 (N=748)	>150 (N=1804)	Placebo (N=3492)
Age (years), median (Q1, Q3)	63.0 (56.0, 69.0)	63.0 (56.0, 68.0)	64.0 (58.0, 70.0)	64.0 (57.0, 69.0)
Female, n (%)	284 (29.3)	179 (23.9)	503 (27.9)	984 (28.2)
Non-white, n (%)	81 (8.4)	49 (6.6)	154 (8.5)	276 (7.9)
CV risk category, n (%)				
Established CV disease	665 (68.6)	538 (71.9)	1317 (73.0)	2500 (71.6)
Diabetes + risk factors	305 (31.4)	210 (28.1)	487 (27.0)	992 (28.4)
Weight (kg), median (Q1, Q3)	93.0 (82.0, 108.0)	95.3 (83.6, 108.7)	90.0 (80.0, 100.0)	92.0 (81.6, 104.3)
BMI (kg/m^2), median (Q1, Q3)	31.6 (28.4, 35.7)	31.9 (28.6, 35.6)	30.2 (27.5, 33.7)	31.0 (28.0, 34.7)
Type 2 diabetes, n (%)	580 (59.8)	436 (58.3)	977 (54.2)	1976 (56.6)
Hypertension, n (%)	878 (90.5)	651 (87.0)	1493 (82.8)	3024 (86.6)
Metabolic syndrome, n (%)	913 (94.1)	701 (93.7)	1655 (91.7)	3209 (91.9)
TG (mg/dL), median (Q1, Q3)	213.0 (173.5, 266.5)	209.0 (173.0, 259.8)	222.5 (181.5, 280.5)	216.0 (176.0, 273.5)
LDL-C (mg/dL), median (Q1, Q3)	75.0 (61.5, 89.0)	72.0 (61.0, 85.0)	75.0 (63.0, 89.0)	76.0 (63.0, 89.0)
HDL-C (mg/dL), median (Q1, Q3)	39.0 (33.5, 45.5)	39.0 (34.0, 45.0)	40.5 (35.5, 46.0)	40.0 (35.0, 46.0)

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RESULTS (cont.)

REDUCE-IT Baseline Medications by Icosapent Ethyl Estimated Average On-treatment EPA or Placebo

	Icosapent Ethyl Estimated Average EPA (µg/mL)			
Medication Taken at Baseline, n (%)	≤100 (N=970)	>100 to ≤150 (N=748)	>150 (N=1804)	Placebo (N=3492)
Anti-diabetes	535 (55.2)	403 (53.9)	906 (50.2)	1837 (52.6)
Anti-hypertensive	942 (97.1)	718 (96.0)	1702 (94.3)	3338 (95.6)
Anti-platelet	778 (80.2)	623 (83.3)	1443 (80.0)	2782 (79.7)
One anti-platelet	581 (59.9)	446 (59.6)	1095 (60.7)	2086 (59.7)
Two or more anti-platelets	197 (20.3)	177 (23.7)	348 (19.3)	696 (19.9)
Anticoagulant	86 (8.9)	75 (10.0)	169 (9.4)	337 (9.7)
Anticoagulant plus anti-platelet	32 (3.3)	28 (3.7)	51 (2.8)	115 (3.3)
No antithrombotic	138 (14.2)	78 (10.4)	243 (13.5)	488 (14.0)
ACE or ARB	781 (80.5)	600 (80.2)	1365 (75.7)	2736 (78.4)
ACE	527 (54.3)	412 (55.1)	902 (50.0)	1844 (52.8)
ARB	268 (27.6)	195 (26.1)	491 (27.2)	941 (26.9)
Beta blockers	704 (72.6)	544 (72.7)	1274 (70.6)	2495 (71.4)
Statins	969 (99.9)	747 (99.9)	1803 (99.9)	3480 (99.7)

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RESULTS (cont.)

IPE Effects on New Heart Failure May Be Mediated by Higher Achieved Serum EPA Concentrations

Endpoint/Subgroup	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	Log-Rank P-value	Trend P-value (Log-Rank)
By IPE Est. Avg. EPA (µg/mL)	*n/N (%)*	*n/N (%)*	*HR (95% CI)*		
New Heart Failure	169/4089 (4.1)	176/4090 (4.3)	0.95 (0.77, 1.17)	0.63	
≤100 vs. placebo	43/972 (4.4)	160/3492 (4.6)	1.08 (0.77, 1.52)	0.59	0.18
>100 to ≤150 vs. placebo	32/748 (4.3)	160/3492 (4.6)	0.93 (0.64, 1.36)	0.72	
>150 vs. placebo	67/1802 (3.7)	160/3492 (4.6)	0.76 (0.57, 1.01)	0.05	
New Heart Failure Requiring Hospitalization	141/4089 (3.4)	144/4090 (3.5)	0.97 (0.77, 1.22)	0.78	
≤100 vs. placebo	36/970 (3.7)	132/3492 (3.8)	1.09 (0.75, 1.58)	0.63	0.24
>100 to ≤150 vs. placebo	26/748 (3.5)	132/3492 (3.8)	0.92 (0.60, 1.40)	0.70	
>150 vs. placebo	55/1804 (3.0)	132/3492 (3.8)	0.75 (0.55, 1.03)	0.07	
New Heart Failure/Cardiovascular (CV) Death	306/4089 (7.5)	346/4090 (8.5)	0.87 (0.75, 1.02)	0.08	
≤100 vs. placebo	76/972 (7.8)	284/3492 (8.1)	1.02 (0.79, 1.32)	0.84	0.002
>100 to ≤150 vs. placebo	49/748 (6.6)	284/3492 (8.1)	0.80 (0.59, 1.09)	0.15	
>150 vs. placebo	103/1802 (5.7)	284/3492 (8.1)	0.67 (0.53, 0.83)	0.0003	
New Heart Failure Requiring Hospitalization/CV Death	281/4089 (6.9)	317/4090 (7.8)	0.87 (0.74, 1.03)	0.10	
≤100 vs. placebo	70/970 (7.2)	258/3492 (7.4)	1.03 (0.79, 1.34)	0.85	0.003
>100 to ≤150 vs. placebo	43/748 (5.7)	258/3492 (7.4)	0.77 (0.56, 1.07)	0.12	
>150 vs. placebo	93/1804 (5.2)	258/3492 (7.4)	0.66 (0.52, 0.84)	0.0006	

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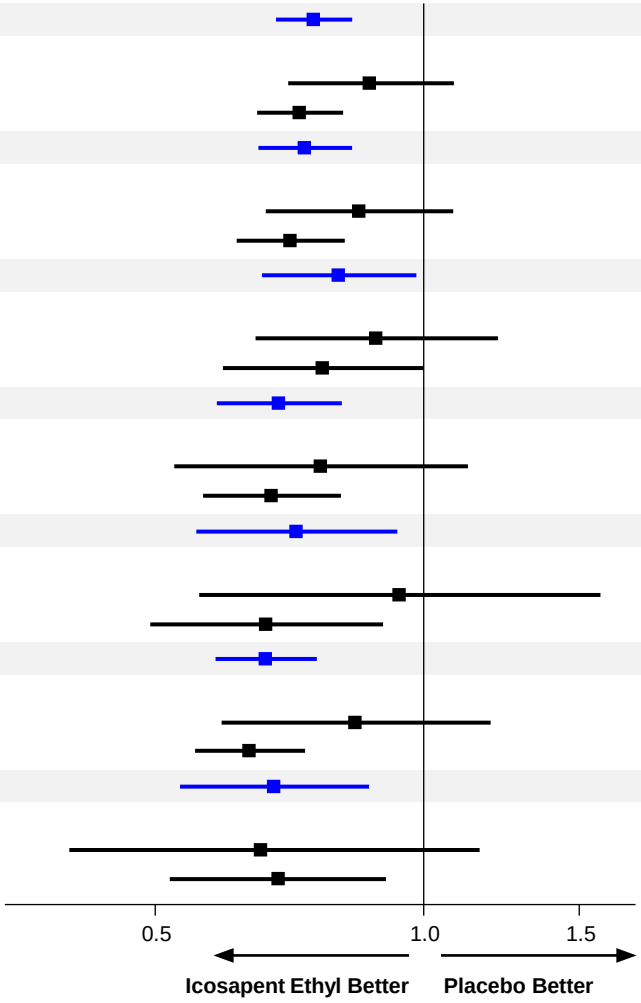
RESULTS (cont.)

Efficacy in Patients with a History of Heart Failure: Similar CV Benefits were Observed in Patients with or without a History of Heart Failure

Endpoint/Subgroup	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	Interaction P-value
	n/N (%)	*n/N (%)*	*HR (95% CI)*	
Primary Composite Endpoint	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68, 0.83)	
History of heart failure				
Yes	160/703 (22.8)	187/743 (25.2)	0.87 (0.70, 1.08)	0.13
No	545/3386 (16.1)	714/3344 (21.4)	0.73 (0.65, 0.81)	
Key Secondary Composite Endpoint	459/4089 (11.2)	606/4090 (14.8)	0.74 (0.65, 0.83)	
History of heart failure				
Yes	119/703 (16.9)	145/743 (19.5)	0.85 (0.66, 1.08)	0.21
No	340/3386 (10.0)	461/3344 (13.8)	0.71 (0.62, 0.81)	
Cardiovascular Death	174/4089 (4.3)	213/4090 (5.2)	0.80 (0.66, 0.98)	
History of heart failure				
Yes	72/703 (10.2)	85/743 (11.4)	0.89 (0.65, 1.21)	0.50
No	102/3386 (3.0)	128/3344 (3.8)	0.77 (0.59, 1.00)	
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1)	355/4090 (8.7)	0.69 (0.58, 0.81)	
History of heart failure				
Yes	46/703 (6.5)	63/743 (8.5)	0.77 (0.52, 1.12)	0.56
No	204/3386 (6.0)	292/3344 (8.7)	0.67 (0.56, 0.81)	
Fatal or Nonfatal Stroke	98/4089 (2.4)	134/4090 (3.3)	0.72 (0.55, 0.93)	
History of heart failure				
Yes	27/703 (3.8)	30/743 (4.0)	0.94 (0.56, 1.58)	0.26
No	71/3386 (2.1)	104/3344 (3.1)	0.67 (0.49, 0.90)	
Coronary Revascularization	376/4089 (9.2)	544/4090 (13.3)	0.66 (0.58, 0.76)	
History of heart failure				
Yes	58/703 (8.3)	72/743 (9.7)	0.84 (0.59, 1.18)	0.14
No	318/3386 (9.4)	472/3344 (14.1)	0.64 (0.55, 0.73)	
Unstable Angina	108/4089 (2.6)	157/4090 (3.8)	0.68 (0.53, 0.87)	
History of heart failure				
Yes	20/703 (2.8)	32/743 (4.3)	0.66 (0.37, 1.15)	0.90
No	88/3386 (2.6)	125/3344 (3.7)	0.69 (0.52, 0.90)	



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RESULTS (cont.)

Efficacy in Patients with a History of Heart Failure: Similar CV Benefits were Observed in Patients with or without a History of Heart Failure (1 of 2)

Endpoint/Subgroup	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	Int. P-value
	n/N (%)	*n/N (%)*	*HR (95% CI)*	
Primary Composite Endpoint	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68, 0.83)	
History of heart failure				
Yes	160/703 (22.8)	187/743 (25.2)	0.87 (0.70, 1.08)	0.13
No	545/3386 (16.1)	714/3344 (21.4)	0.73 (0.65, 0.81)	
Key Secondary Composite Endpoint	459/4089 (11.2)	606/4090 (14.8)	0.74 (0.65, 0.83)	
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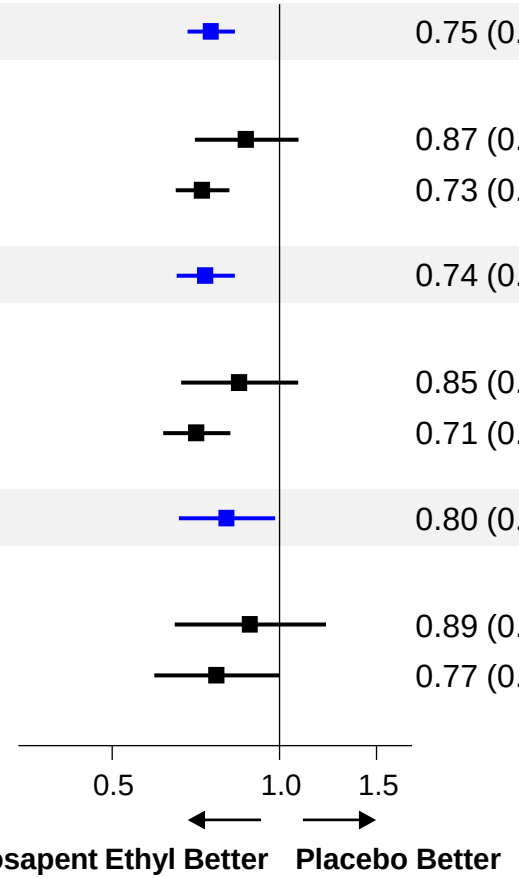

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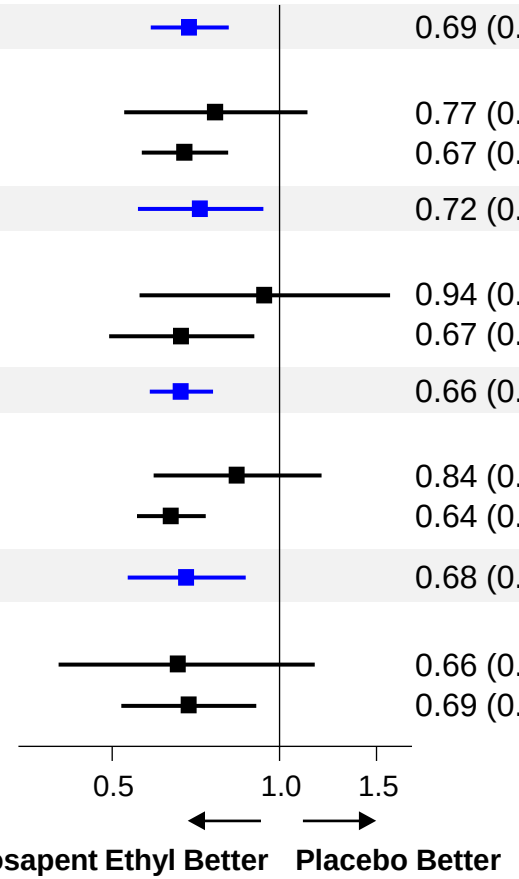
RESULTS (cont.)

Efficacy in Patients with a History of Heart Failure: Similar CV Benefits were Observed in Patients with or without a History of Heart Failure (2 of 2)

Endpoint/Subgroup	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	Int. P-value
	n/N (%)	*n/N (%)*	*HR (95% CI)*	
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1)	355/4090 (8.7)	0.69 (0.58, 0.81)	
History of heart failure				
Yes	46/703 (6.5)	63/743 (8.5)	0.77 (0.52, 1.12)	0.56
No	204/3386 (6.0)	292/3344 (8.7)	0.67 (0.56, 0.81)	
Fatal or Nonfatal Stroke	98/4089 (2.4)	134/4090 (3.3)	0.72 (0.55, 0.93)	
History of heart failure				
Yes	27/703 (3.8)	30/743 (4.0)	0.94 (0.56, 1.58)	0.26
No	71/3386 (2.1)	104/3344 (3.1)	0.67 (0.49, 0.90)	
Coronary Revascularization	376/4089 (9.2)	544/4090 (13.3)	0.66 (0.58, 0.76)	
History of heart failure				
Yes	58/703 (8.3)	72/743 (9.7)	0.84 (0.59, 1.18)	0.14
No	318/3386 (9.4)	472/3344 (14.1)	0.64 (0.55, 0.73)	
Unstable Angina	108/4089 (2.6)	157/4090 (3.8)	0.68 (0.53, 0.87)	
History of heart failure				
Yes	20/703 (2.8)	32/743 (4.3)	0.66 (0.37, 1.15)	0.90
No	88/3386 (2.6)	125/3344 (3.7)	0.69 (0.52, 0.90)	



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SAFETY

- 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 the small numbers of hemorrhagic stroke.
- More atrial fibrillation/flutter occurred with icosapent ethyl versus placebo.

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LIMITATIONS

- These data include both pre-specified and *post hoc* analyses.
- Heart failure was a prespecified tertiary endpoint within **REDUCE-IT**.
- ~14% of the patients did not have baseline EPA levels
  - Baseline characteristics and outcomes in those with/without missing data were similar
- On-treatment EPA values were estimated from available annual serum samples.

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CONCLUSIONS

- In the full population, compared with placebo, icosapent ethyl 4 g/day did not reduce new heart failure or new heart failure requiring hospitalization.
- Patients with a history of heart failure observed similar cardiovascular risk reduction as patients without.
- New heart failure may be reduced in patients who achieve serum EPA levels higher than ~150 µg/mL, though this needs to be tested prospectively.

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DISCLOSURES

REDUCE-IT was sponsored by Amarin Pharma, Inc.

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.

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REFERENCES

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