ACC Latin America Conference 2018

In partnership with:

TOP CLINICAL TRIALS of 2018 to Impact Your Practice - ASCEND (& REDUCE IT)

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Disclosure of Potential Conflicts of Interest (David Brasil)

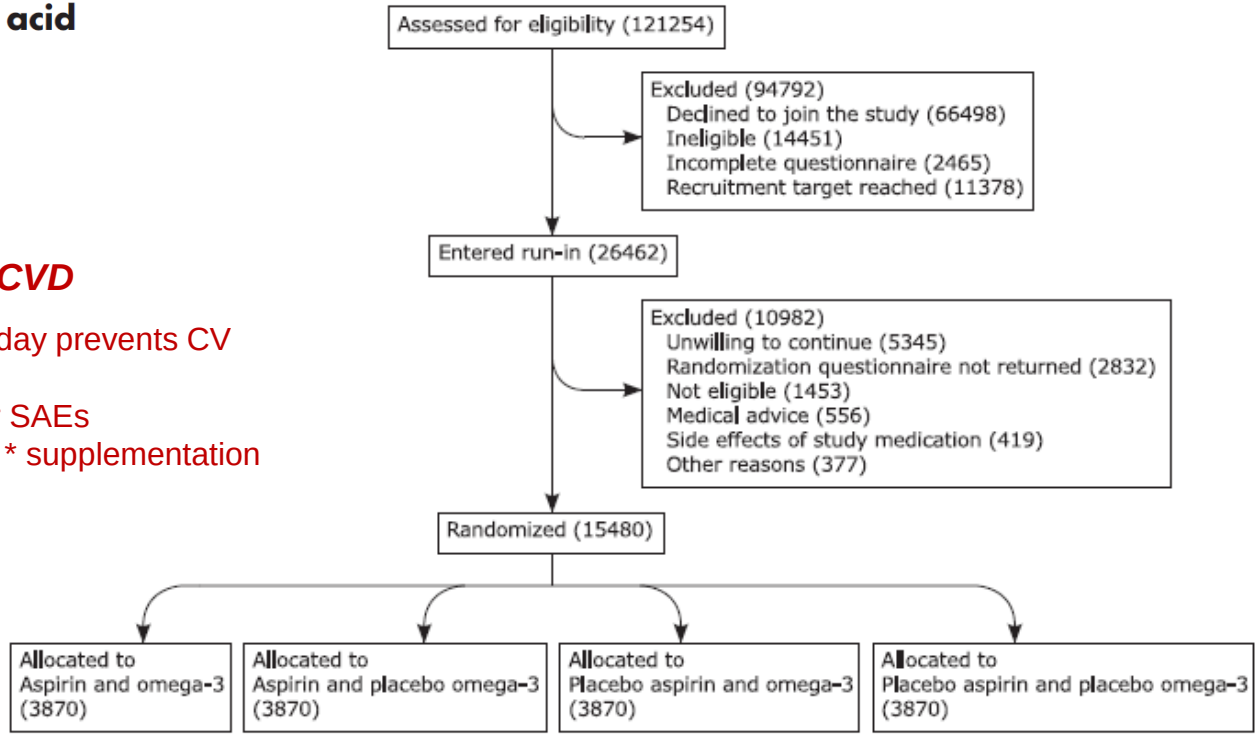
Categories of potential conflicts of interest	Company (2016, 2017 and 2018)
Sponsored in transport and/or hotel accommodations in Congresses/Conferences	**Servier**
Sponsored in clinical trials and/or in basic research funded by pharmaceutical companies	**Bayer - National Lead Investigator Voyager-PAD Clinical Trial**
Speaker in meetings sponsored by pharmaceutical companies	**Servier, LIBBS**
Participate in normative committees of scientific trials sponsored by pharmaceutical companies	**Bayer - National Lead Investigator & member of the International Steering Committee Voyager-PAD Clinical Trial**
Receive institutional support from pharmaceutical companies	–
Writing of educative materials sponsored by pharmaceutical companies	**LIBBS, Servier**
Provide training in evidence-based medicine for pharmaceutical company's personnel	**Vertex**
Hold stocks of pharmaceutical companies	–

ASCEND: A Study of Cardiovascular Events iN Diabetes: Characteristics of a randomized trial of aspirin and of omega-3 fatty acid supplementation in 15,480 people with diabetes

Bowman *et al. Am Heart J* 2018;198:135-144. Epub 2017 Dec 24.

✓ *AIM: primary prevention of CVD*

- ☑ To determine whether Aspirin 100 mg/day prevents CV events or cancer in patients with DM
- ☑ To assess significant bleeding or other SAEs
- ☑ To assess whether omega-3 fatty acid * supplementation prevents CVD



Trial profile: Flow of participants through the ASCEND trial.

*** Omega-3 Fatty Acid Supplement:**
Capsules of 1g/day containing 90% O-3FA =
0.41g eicosapentaenoic acid + 0.34g docosahexaenoic acid

ASCEND: A Study of Cardiovascular Events iN Diabetes: Characteristics of a randomized trial of aspirin and of omega-3 fatty acid supplementation in 15,480 people with diabetes

Bowman *et al. Am Heart J* 2018;198:135-144. Epub 2017 Dec 24.

✓ *Inclusion/Exclusion Criteria:*

- ☑ Clinical diagnosis of T1DM or T2DM (*standard ADA or WHO diagnosis criteria*)
- ☑ No clear ***indication*** for aspirin (*i.e.*, no diagnosis of occlusive arterial disease)
- ☑ No clear ***contra-indication*** to aspirin (*i.e.*, high risk of bleeding due GI hemorrhage or peptic ulcer within the previous 6 months; active hepatic disease; use of warfarin or other anti-coagulant therapy; no history of aspirin allergy)
- ☑ Substantial uncertainty about whether antiplatelet or O-3FA therapy confers worthwhile benefit (*i.e.*, patient or GP did not consider use aspirin or O-3FA regularly)
- ☑ No other predominant life-threatening medical problem (other than DM) that might prevent patients from taking at least 5 years of study treatment.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

✓ **BASELINE CHARACTERISTICS**
Aspirin Groups

ASCEND Study Collaborative Group, Bowman *et al*.
N Engl J Med 2018;379(16):1529-1539. Epub 2018 Aug 26.

Table 1. Key Characteristics of the Participants at Baseline.*

Characteristic	Aspirin Group (N=7740)	Placebo Group (N=7740)
Age		
Mean — yr	63.2±9.2	63.3±9.2
Distribution — no. (%)		
<60 yr	2795 (36.1)	2795 (36.1)
60 to <70 yr	3123 (40.3)	3124 (40.4)
≥70 yr	1822 (23.5)	1821 (23.5)
Male sex — no. (%)	4843 (62.6)	4841 (62.5)
White race — no. (%)†	7467 (96.5)	7468 (96.5)
Body-mass index‡		
Mean	30.8±6.2	30.6±6.3
Distribution — no. (%)		
<25	1080 (14.0)	1169 (15.1)
25 to <30	2753 (35.6)	2776 (35.9)
≥30	3665 (47.4)	3536 (45.7)
Unknown	242 (3.1)	259 (3.3)
Smoking status — no. (%)		
Current smoker	639 (8.3)	640 (8.3)
Former smoker	3526 (45.6)	3525 (45.5)
Never smoked	3489 (45.1)	3488 (45.1)
Unknown	86 (1.1)	87 (1.1)
Participant-reported hypertension — no. (%)	4766 (61.6)	4767 (61.6)
Aspirin use before screening — no. (%)	2740 (35.4)	2768 (35.8)
Statin use — no. (%)	5854 (75.6)	5799 (74.9)
Type 2 diabetes — no. (%)§	7282 (94.1)	7287 (94.1)
Duration of diabetes		
Median (interquartile range) — yr	7 (3–13)	7 (3–13)
Distribution — no. (%)		
<9 yr	4337 (56.0)	4322 (55.8)
≥9 yr	2976 (38.4)	2989 (38.6)
Unknown	427 (5.5)	429 (5.5)
Systolic blood pressure		
Mean — mm Hg	136.1±15.2	136.2±15.3
Distribution — no. (%)		
<130 mm Hg	1694 (21.9)	1700 (22.0)
≥130 to <140 mm Hg	1550 (20.0)	1541 (19.9)
≥140 mm Hg	2263 (29.2)	2292 (29.6)
Unknown	2233 (28.9)	2207 (28.5)
Vascular risk score — no. (%)¶		
Low	3128 (40.4)	3136 (40.5)
Moderate	3294 (42.6)	3254 (42.0)
High	1318 (17.0)	1350 (17.4)

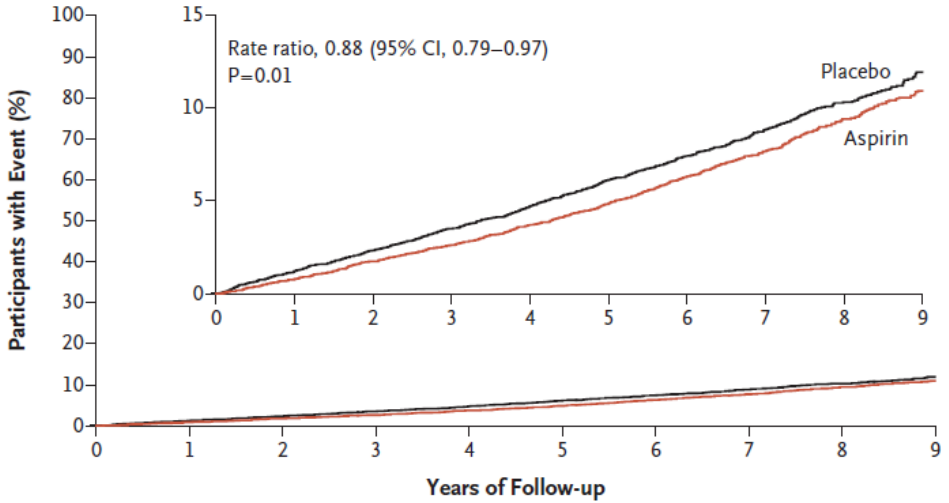
ASPIRIN

✓ *RESULTS*

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

A First Serious Vascular Event



No. at Risk										
Placebo	7740	7618	7486	7342	7188	7001	5771	3890	2200	1430
Aspirin	7740	7655	7536	7404	7252	7096	5825	3966	2222	1428
Cumulative benefit per 1000 participants in aspirin group		4±2	6±2	9±3	10±3	13±4	11±4	12±5	9±6	10±7

First serious vascular event is the composite of:

- nonfatal MI,
- nonfatal ischemic stroke or TIA
- or death from any vascular cause (*excluding confirmed intracranial hemorrhage*)

ASCEND Study Collaborative Group, Bowman *et al*. *N Engl J Med* 2018;379(16):1529-1539. Epub 2018 Aug 26.

ASPIRIN

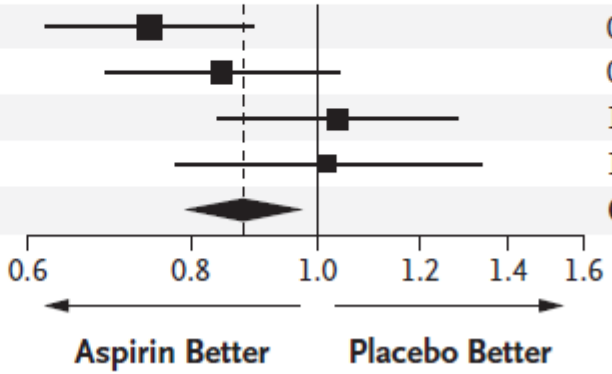
✓ *RESULTS*

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

B First Serious Vascular Event, According to Year of Follow-up

Year of First Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
<3	201 (2.6)	269 (3.5)	0.74 (0.62–0.89)	
3 to <5	169 (2.3)	198 (2.7)	0.85 (0.69–1.04)	
≥5 to <7	180 (2.5)	171 (2.4)	1.04 (0.84–1.28)	
7	108 (2.7)	105 (2.7)	1.02 (0.78–1.33)	
All	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**



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ASPIRIN

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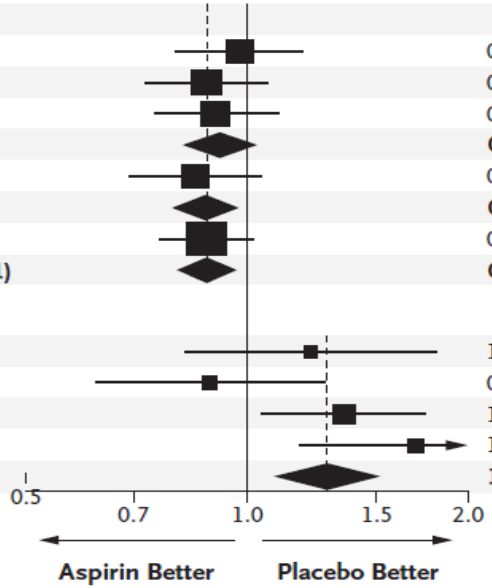
Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Vascular Outcomes				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80–1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73–1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75–1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82–1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69–1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76–1.02)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**	
Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**



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ASPIRIN

✓ **CANCER RESULTS**

Table 2. Effect of Aspirin Use on the Incidence of Site-Specific Fatal or Nonfatal Cancer.*

Cancer Type	Aspirin Group (N = 7740)	Placebo Group (N = 7740)	Rate Ratio (95% CI)
	no. of participants (%)		
Gastrointestinal tract cancer	157 (2.0)	158 (2.0)	0.99 (0.80–1.24)
Other gastrointestinal cancer†	87 (1.1)	82 (1.1)	1.06 (0.78–1.43)
Respiratory cancer	101 (1.3)	103 (1.3)	0.98 (0.74–1.29)
Genitourinary cancer	332 (4.3)	294 (3.8)	1.13 (0.97–1.32)
Hematologic cancer	88 (1.1)	86 (1.1)	1.02 (0.76–1.38)
Breast cancer	97 (1.3)	96 (1.2)	1.01 (0.76–1.34)
Melanoma	50 (0.6)	59 (0.8)	0.85 (0.58–1.23)
Other cancer	25 (0.3)	30 (0.4)	0.83 (0.49–1.41)
Unspecified cancer	26 (0.3)	31 (0.4)	0.84 (0.50–1.41)
Any cancer‡	897 (11.6)	887 (11.5)	1.01 (0.92–1.11)

ASCEND Study Collaborative Group, Bowman *et al*. *N Engl J Med* 2018;379(16):1529-1539. Epub 2018 Aug 26.

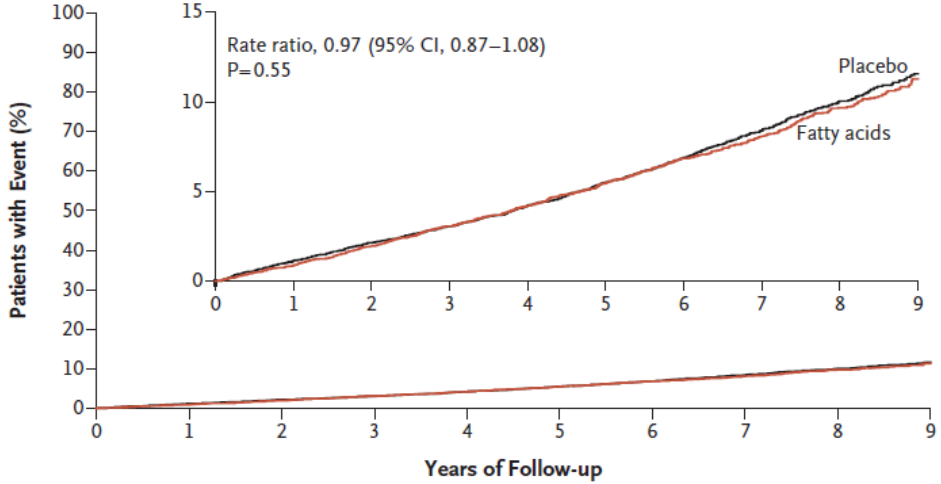
n-3Fatty Acid Suppl

✓ *RESULTS*

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*

A First Serious Vascular Event



No. at Risk										
Placebo	7740	7627	7503	7377	7222	7047	5792	3934	2224	1428
Fatty acids	7740	7646	7519	7369	7218	7050	5804	3922	2198	1430
Cumulative benefit per 1000 patients in fatty acid group		3±2	2±2	0±3	0±3	0±4	1±4	3±5	4±6	3±7

First serious vascular event is the composite of:

- nonfatal MI,
- nonfatal ischemic stroke or TIA
- or death from any vascular cause (*excluding confirmed intracranial hemorrhage*)

ASCEND Study Collaborative Group, Bowman *et al*. *N Engl J Med* 2018;379(16):1540-1550. Epub 2018 Aug 26.

n-3Fatty Acid Suppl

✓ *RESULTS*

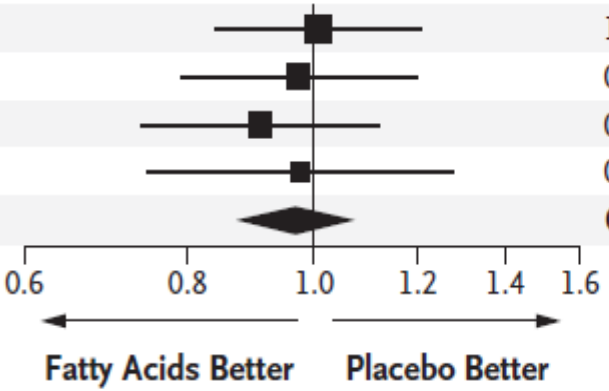
Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*

B First Serious Vascular Event, According to Year of Follow-up

Year of First Event	Fatty Acids (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of patients with event (%)			
<3	236 (3.0)	234 (3.0)	1.01 (0.84–1.21)	
3 to <5	181 (2.5)	186 (2.5)	0.97 (0.79–1.20)	
5 to <7	167 (2.4)	184 (2.6)	0.91 (0.74–1.12)	
≥7	105 (2.7)	108 (2.7)	0.98 (0.75–1.28)	
All	**689 (8.9)**	**712 (9.2)**	**0.97 (0.87–1.08)**	**0.55**

Test for trend across years χ^2=0.22 (P=0.64)



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N Engl J Med 2018;379(16):1540-1550. Epub 2018 Aug 26.

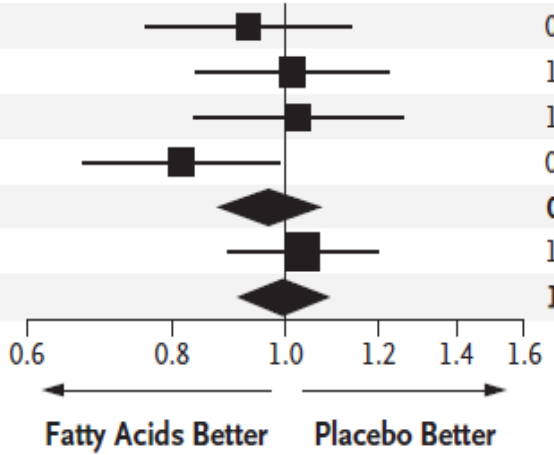
n-3Fatty Acid Suppl

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*

✓ ***RESULTS: Separate Components of Primary Endpoint***

Type of Event	Fatty Acids (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of patients with event (%)			
Nonfatal myocardial infarction	186 (2.4)	200 (2.6)	0.93 (0.76–1.14)	
Nonfatal ischemic stroke	217 (2.8)	214 (2.8)	1.01 (0.84–1.22)	
Transient ischemic attack	185 (2.4)	180 (2.3)	1.03 (0.84–1.26)	
Vascular death	186 (2.4)	228 (2.9)	0.81 (0.67–0.99)	
Serious vascular event	**689 (8.9)**	**712 (9.2)**	**0.97 (0.87–1.08)**	**0.55**
Any revascularization	368 (4.8)	356 (4.6)	1.04 (0.90–1.20)	
Serious vascular event or revascularization	**882 (11.4)**	**887 (11.5)**	**1.00 (0.91–1.09)**	



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N Engl J Med 2018;379(16):1540-1550. Epub 2018 Aug 26.

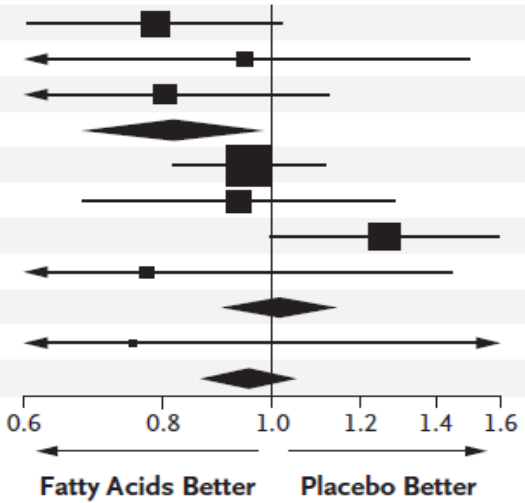
n-3Fatty Acid Suppl

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*

✓ ***RESULTS: Death from vascular and other causes***

Cause of Death	Fatty Acids (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)
	no. of patients with event (%)		
Coronary	100 (1.3)	127 (1.6)	0.79 (0.61–1.02)
All stroke	35 (0.5)	37 (0.5)	0.94 (0.59–1.50)
Other vascular	61 (0.8)	76 (1.0)	0.80 (0.57–1.12)
Vascular	**196 (2.5)**	**240 (3.1)**	**0.82 (0.68–0.98)**
Cancer	305 (3.9)	319 (4.1)	0.95 (0.82–1.12)
Respiratory	73 (0.9)	78 (1.0)	0.93 (0.68–1.28)
Other medical	158 (2.0)	125 (1.6)	1.26 (1.00–1.59)
External causes	17 (0.2)	22 (0.3)	0.77 (0.41–1.45)
Nonvascular	**553 (7.1)**	**544 (7.0)**	**1.01 (0.90–1.14)**
Unknown cause	3 (0.0)	4 (0.1)	0.75 (0.17–3.31)
All causes	**752 (9.7)**	**788 (10.2)**	**0.95 (0.86–1.05)**



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DOI 10.1002/clc.22692

PREVENTION WILEY CLINICAL CARDIOLOGY

TRIAL DESIGNS

Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

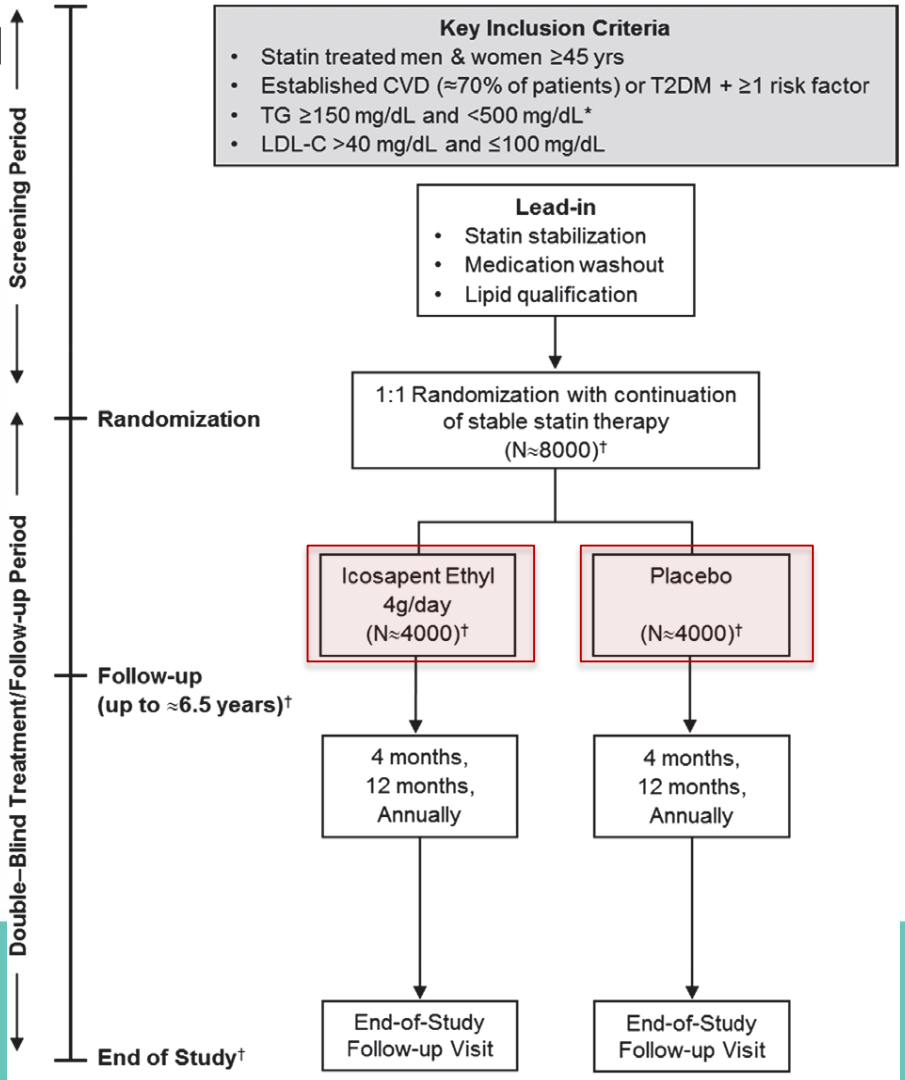
Question: Does lowering TG on top of statin therapy improve CV outcomes?

Phase 3b RCT, double-blinded, placebo-controlled trial
Icosapent ethyl 4g/day
(a highly purified ethyl ester of EPA)
versus
Placebo

Primary Endpoint: a composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or UA

n = 8,179 event-driven trial (until approximately 1612 adjudicated primary-efficacy endpoint events)

Bhatt *et al* on behalf of the REDUCE-IT Investigators.
Clin Cardiol 2017;40:138-148.



REDUCE-IT™ Cardiovascular Outcomes Study of Vascepa® (icosapent ethyl) Capsules Met Primary Endpoint

September 24, 2018

REDUCE-IT Is First Outcomes Study to Assess Treatment of Patients with LDL-C Controlled by Statin Therapy, Persistent Elevated Triglycerides and Other Cardiovascular Risk Factors

Results Specific to Pure EPA Vascepa at 4 Grams Daily

- Efficacy: Approximately 25% relative risk reduction, demonstrated to a high degree of statistical significance (p<0.001), in the primary endpoint composite of the first occurrence of MACE, including cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization. This result was supported by robust demonstrations of efficacy across multiple secondary endpoints.

  REDUCE-IT met its *primary endpoint* with approximately 25% RRR (p<0.001) in MACEs in the intent-to-treat patient population

- Safety: Vascepa was well tolerated with a safety profile consistent with clinical experience associated with omega-3 fatty acids and current FDA-approved labeling. The proportions of patients experiencing adverse events and serious adverse events in REDUCE-IT were similar between the active and placebo treatment groups. Median follow-up time in REDUCE-IT was 4.9 years.

  “robust demonstrations of efficacy across multiple secondary endpoints”

Amarin is eager to share REDUCE-IT data in greater detail with both the medical community and regulatory authorities. REDUCE-IT results have been accepted for presentation at the 2018 Scientific Sessions of the American Heart Association (AHA) on November 10, 2018 in Chicago, Illinois. The presentation, classified as late breaking clinical trial results, is scheduled to commence at 2:16 pm Central Time and listed as Main Event 1 for the time frame. This acceptance as a presentation of late-breaking clinical trial results was granted based on the ability of REDUCE-IT to address a critical question in cardiovascular prevention.

https://investor.amarincorp.com/news-releases/news-release-details/reduce-ittm-cardiovascular-outcomes-study-vascepar-icosapent

REDUCE-IT™ Cardiovascular Outcomes Study of Vascepa® (icosapent ethyl) Capsules Met Primary Endpoint

September 24, 2018

REDUCE-IT Is First Outcomes Study to Assess Treatment of Patients with LDL-C Controlled by Statin Therapy, Persistent Elevated Triglycerides and Other Cardiovascular Risk Factors

Results Specific to Pure EPA Vascepa at 4 Grams Daily

Conference Call Scheduled for Today, Monday, September 24, 2018 at 8:00 am ET

BEDMINSTER, N.J. and DUBLIN, Ireland, Sept. 24, 2018 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN), announced today topline results from the Vascepa® cardiovascular (CV) outcomes trial, REDUCE-IT™, a global study of 8,179 statin-treated adults with elevated CV risk. REDUCE-IT met its primary endpoint demonstrating an approximately 25% relative risk reduction, to a high degree of statistical significance (p<0.001), in major adverse CV events (MACE) in the intent-to-treat patient population with use of Vascepa 4 grams/day as compared to placebo.

Patients enrolled in REDUCE-IT had LDL-C between 41-100 mg/dL (median baseline LDL-C 75 mg/dL) controlled by statin therapy and various cardiovascular risk factors including persistent elevated triglycerides (TGs) between 150-499 mg/dL (median baseline 216 mg/dL) and either established cardiovascular disease (secondary prevention cohort) or diabetes mellitus and at least one other CV risk factor (primary prevention cohort).

Key topline results include:

- Efficacy: Approximately 25% relative risk reduction, demonstrated to a high degree of statistical significance (p<0.001), in the primary endpoint composite of the first occurrence of MACE, including cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization. This result was supported by robust demonstrations of efficacy across multiple secondary endpoints.
- Safety: Vascepa was well tolerated with a safety profile consistent with clinical experience associated with omega-3 fatty acids and current FDA-approved labeling. The proportions of patients experiencing adverse events and serious adverse events in REDUCE-IT were similar between the active and placebo treatment groups. Median follow-up time in REDUCE-IT was 4.9 years.

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"I look forward to the publication of these detailed REDUCE-IT results in a major peer-reviewed journal and to presenting them at the AHA in November," stated Deepak L. Bhatt, MD, MPH, Professor of Medicine at Harvard Medical School, Executive Director of Interventional Cardiovascular Programs in the Heart and Vascular Center at Brigham and Women's Hospital, and the Principal Investigator and Steering Committee Chair for REDUCE-IT.

"Amarin expresses its great appreciation for all the people that brought REDUCE-IT to completion, especially the patients and investigators and their colleagues at clinical sites that participated in this study for many years," stated Steven Ketchum, PhD, president of research and development and chief scientific officer of Amarin. "Amarin is also grateful to the U.S. Food and Drug Administration (FDA) for its continued encouragement and support toward study design and completion. REDUCE-IT was conducted under a special protocol assessment agreement with FDA that was re-affirmed in 2016."

"We are delighted with these topline study results," said John F. Thero, president and CEO of Amarin. "Given Vascepa is affordably priced, orally administered and has a favorable safety profile, REDUCE-IT results could lead to a new paradigm in treatment to further reduce the significant cardiovascular risk that remains in millions of patients with LDL-C controlled by statin therapy, as studied in REDUCE-IT."

"Considered against the backdrop of multiple unsuccessful cardiovascular outcomes studies of earlier generation drug therapies, including multiple recent failed cardiovascular studies of omega-3 mixture products that contain the omega-3 acid DHA, REDUCE-IT topline results stand alone as positive and confirm our hypothesis that pure EPA Vascepa at 4 grams/day can provide additional cardiovascular risk reduction benefit on top of LDL-C control with standard of care statin therapy in studied patients," added Craig Granowitz, MD, PhD, senior vice president and chief medical officer of Amarin. "REDUCE-IT results cannot be generalized to fenofibrate, fish oil or omega-3 mixture products that contain DHA. The most relevant comparator study to REDUCE-IT is the Japan EPA lipid intervention study (JELIS), the 18,645 patient, open label, blinded endpoint outcomes study of EPA added to low-dose statin therapy, which showed cardiovascular event reduction in Japanese hypercholesterolemic patients of 19% in the overall population and 53% in a subgroup of patients with elevated TG levels and low HDL-C.[1, 2, 3]

Commercial Expansion and Next Steps

As previously described, given the successful topline results of REDUCE-IT, Amarin is in the process of increasing the number of company sales