Jane Armitage
University of Oxford, UK

Relevant disclosures:

Chief investigator of ASCEND: omega-3 FA 1 g vs placebo daily in 15,000 people with diabetes. Research grants to University of Oxford from Solvay/Abbott/Mylan and Bayer (ASCEND)

and from The Medicines Company (ORION 4).

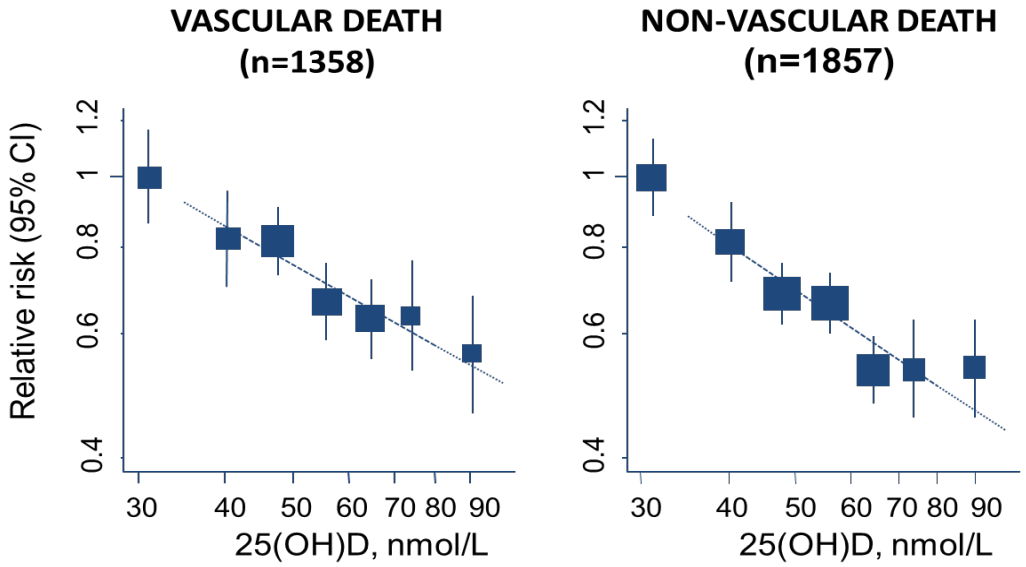
No personal payments from pharmaceutical industry

The VITamin D and OmegA-3 TriaL (VITAL)

- Over 25,000 randomised
- Good balance achieved between groups
- Follow-up for:
  - mortality almost complete
  - morbidity, some loss from non response
- Adherence to interventions was good
- Intention-to-treat analyses
- >90% power to detect 15% reduction in total cancer and 20% in risk of CV events

The VITamin D and OmegA-3 TriaL (VITAL)

Prospective observational relationship between blood marker of vitamin D status and death



After accounting for age, BP, lipids, exercise, frailty etc

2000 IU vitamin D daily likely to raise blood 25(OH) vitamin D by ~50 nmol/l or 20 ng/ml

But with loss of compliance probably about 40 nmol/l (15 ng/ml)

The VITamin D and OmegA-3 TriaL (VITAL)

25,871 middle aged and older adults
randomised and followed for 5.3 years

	Vit D		Placebo	
Major CVD events[a]	396	vs	409	HR 0.97 (0.85-1.12)
Total invasive cancer	793	vs	824	HR 0.96 (0.88-1.06)

([a] MI, stroke, CV death)

Good test of the hypothesis:
robust null result

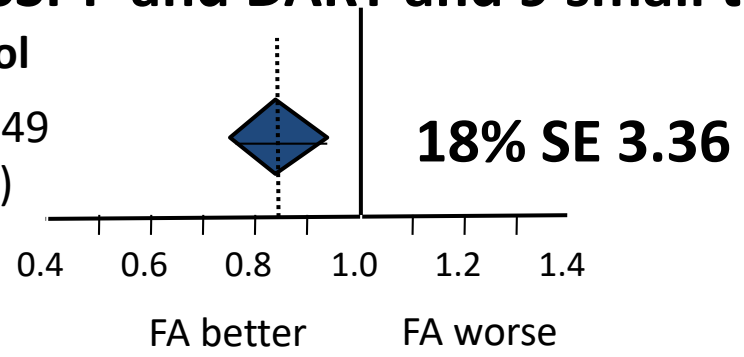
Cancer death 112 vs 149 HR 0.75 (0.59-0.96)
(excluding first 2 years)

NOT SIGNIFICANT after accounting for multiple comparisons

Previous evidence for Omega-3 supplementation

2002: Meta-analysis of trials (GISSI-P and DART and 9 small trials)

	Omega-3	Control
ALL TRIALS (CHD events)	601/7733 (7.7%)	712/7649 (9.3%)



Adapted from Bucher HC et al. Am J Med 2002;112:298-304

2012 Meta-analysis of 10 large trials of Omega-3 fatty acids

77,917 high risk individuals, Aung et al 2018 JAMA

Major vascular events	HR 0.97; 95% CI: 0.93-1.01 p=0.10
CHD death	HR 0.93; 99% CI: 0.83-1.03, p=0.053
Non-fatal MI	HR 0.97; 99% CI: 0.87-1.08 p=0.4

VITAL: Hazard Ratios (HR) and 95% CIs of the CVD Outcomes by Randomized Assignment to Omega-3 Fatty Acids

	Omega-3 FA (N=12,933)	Placebo (N=12,938)	HR	(95% CI)
	No. of Events			
Cardiovascular disease (1°and 2° outcomes)				
Major CVD events[a]	386	419	0.92	(0.80-1.06)
Expanded CVD events[b]	527	567	0.93	(0.82-1.04)
Total MI	145	200	0.72	(0.59-0.90)*
Total stroke	148	142	1.04	(0.83-1.31)
CVD mortality	142	148	0.96	(0.76-1.21)
Other outcomes[c]				
Total invasive cancer	820	797	1.03	(0.93-1.13)
Cancer death	168	173	0.97	(0.79-1.20)
All-cause mortality	493	485	1.02	(0.90-1.15)

*Nominal p-value <0.05.

[a]Primary outcome. A composite of MI, stroke and CVD mortality. [b]A composite of above plus CABG/PCI. [c]Not prespecified as primary or secondary outcomes. [d]A composite of MI, CABG/PCI, and CHD death.

VITAL: a large well done study

- **PRIMARY RESULT** Neither omega-3 FAs nor vitamin D significantly reduced the primary endpoints of major CVD events or total invasive cancer.

ROBUST RESULT

- Omega-3s reduced total MI by 28% (nominal p-value=0.003, Bonferroni-adjusted p-value=0.015)

LESS ROBUST

- Greatest reductions in those with low dietary fish intake and in African Americans.