



Antioxidants and CV disease



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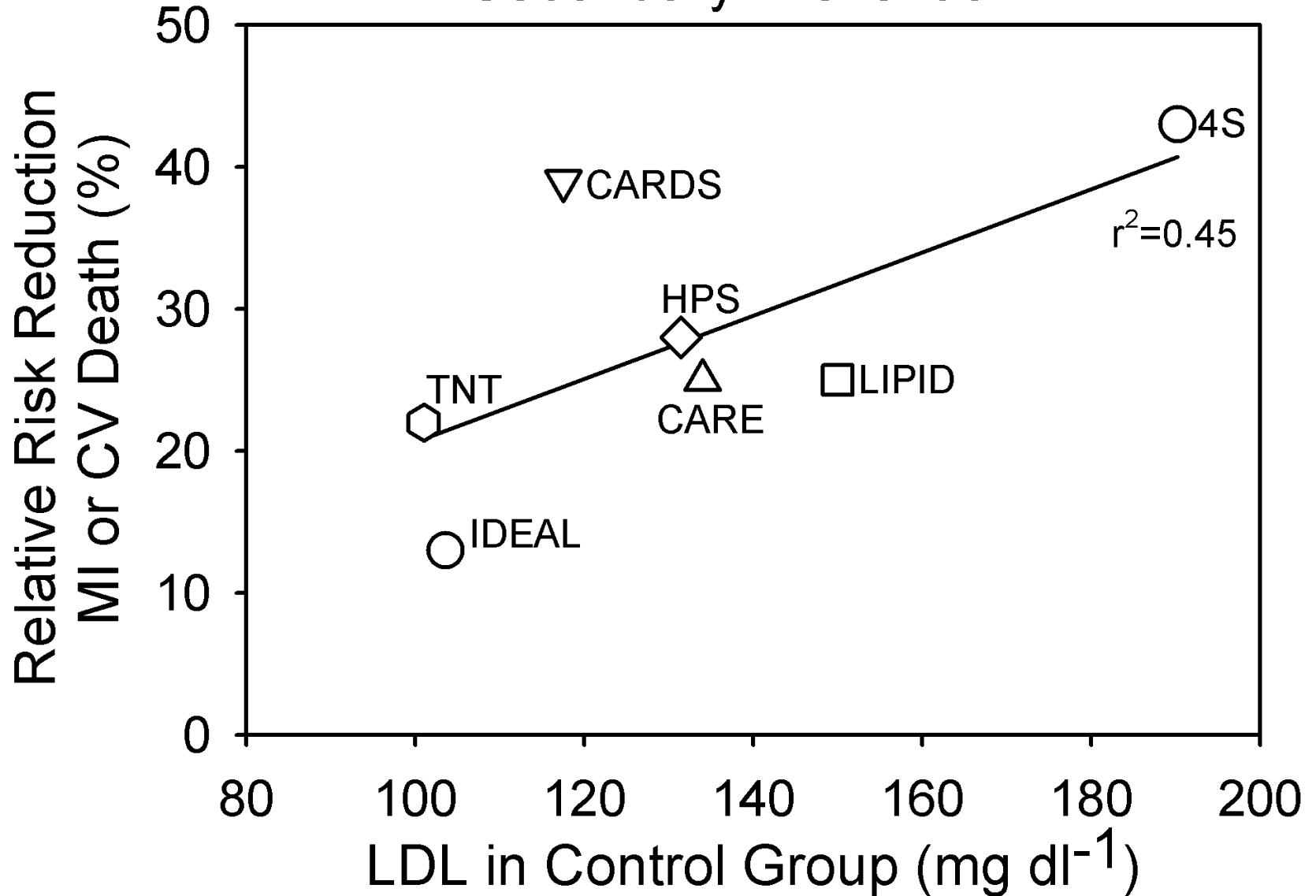
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RRR with Statin Trials Secondary Prevention





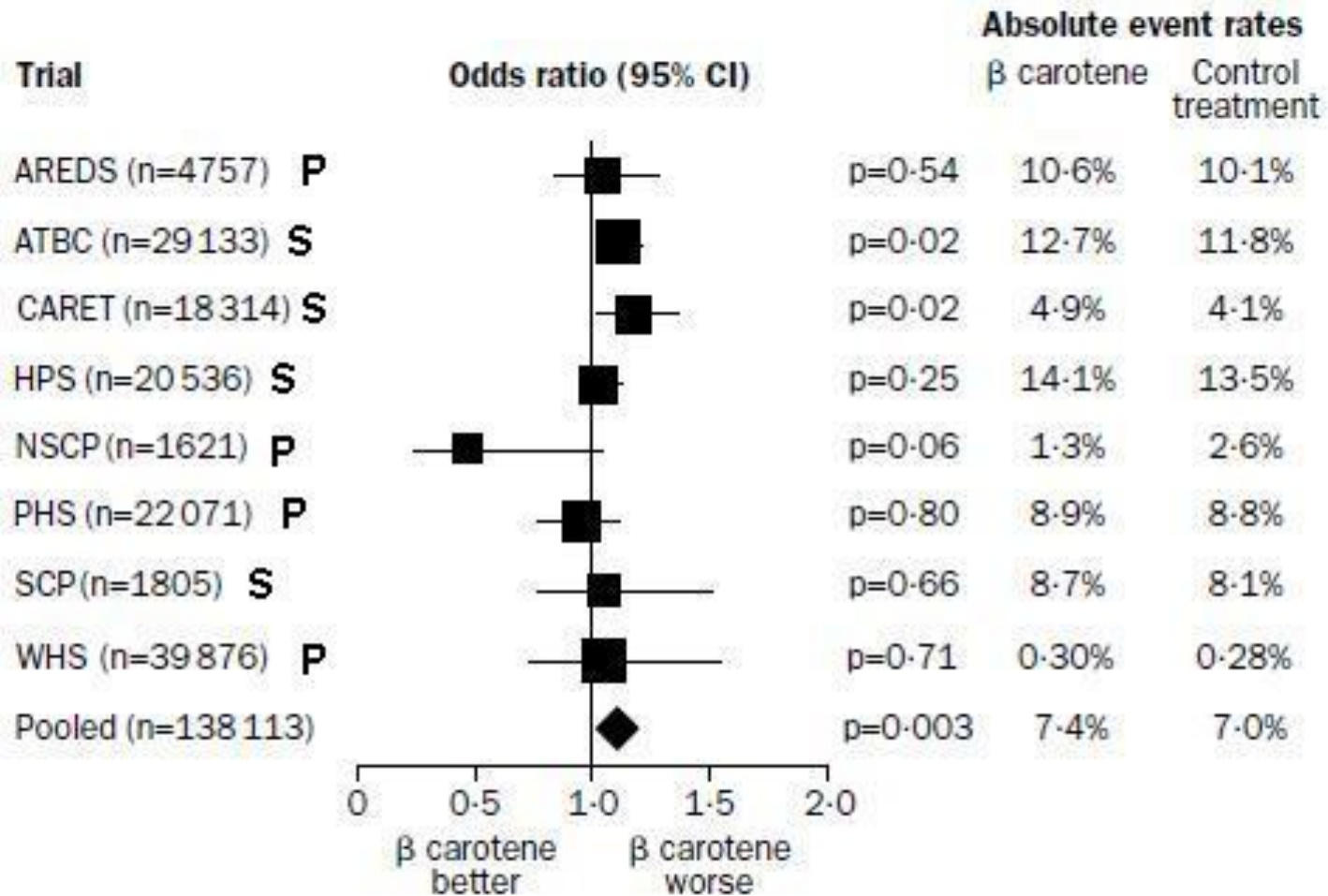
Antioxidants and CV disease

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- Beta carotene
- Vitamin E
- Probuocol
- Succinobuocol
- Diet



No effect on mortality with beta carotene 60-200 mg daily Lancet 361:2017, 2003

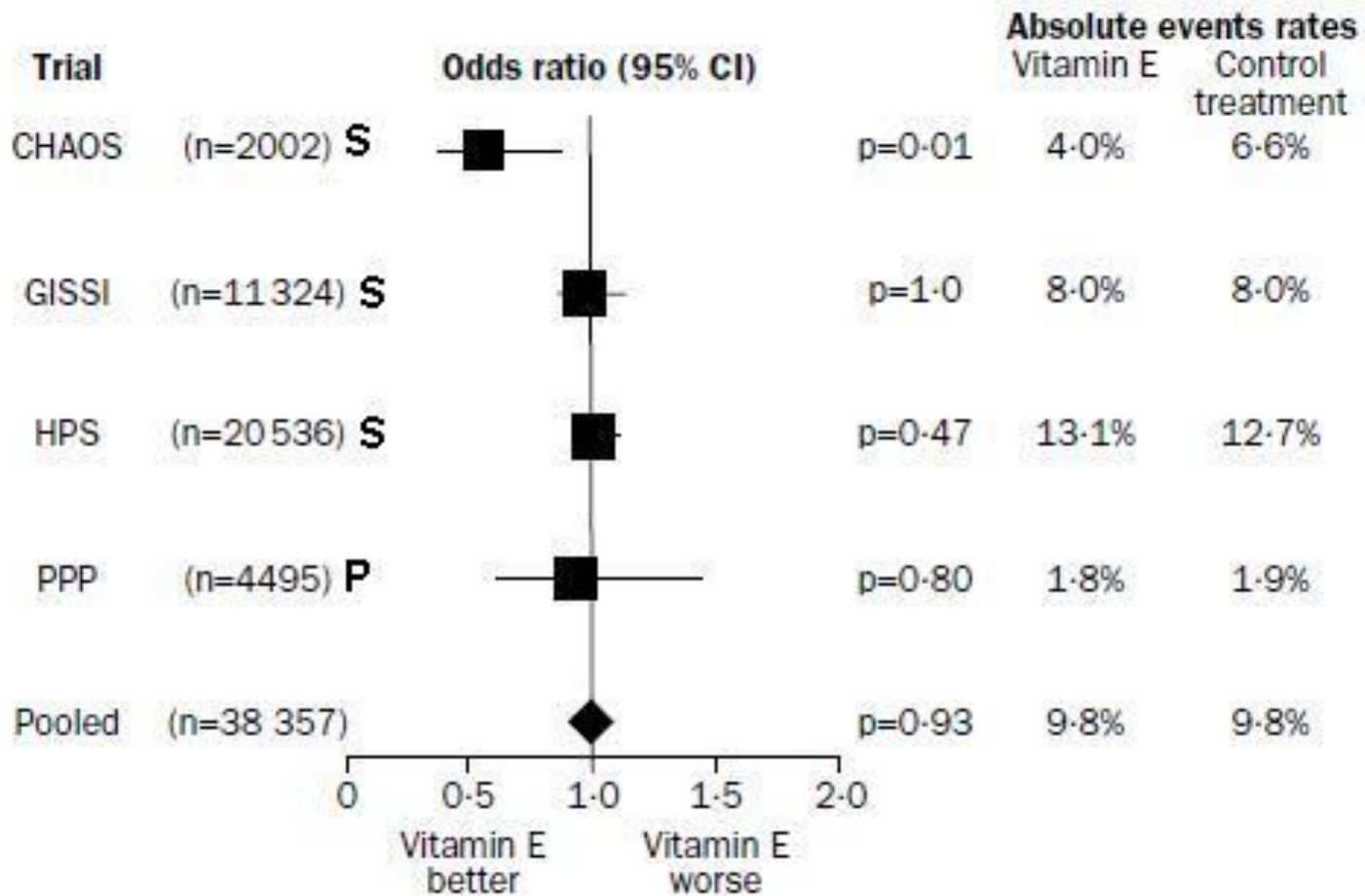


Breslow-Day test: p=0.32

Figure 1: Odds ratios (95% CI) of all-cause mortality for individuals treated with β carotene or control therapy



No effect on MI/CV death with vitamin E 300-800 U daily Lancet 361:2017, 2003



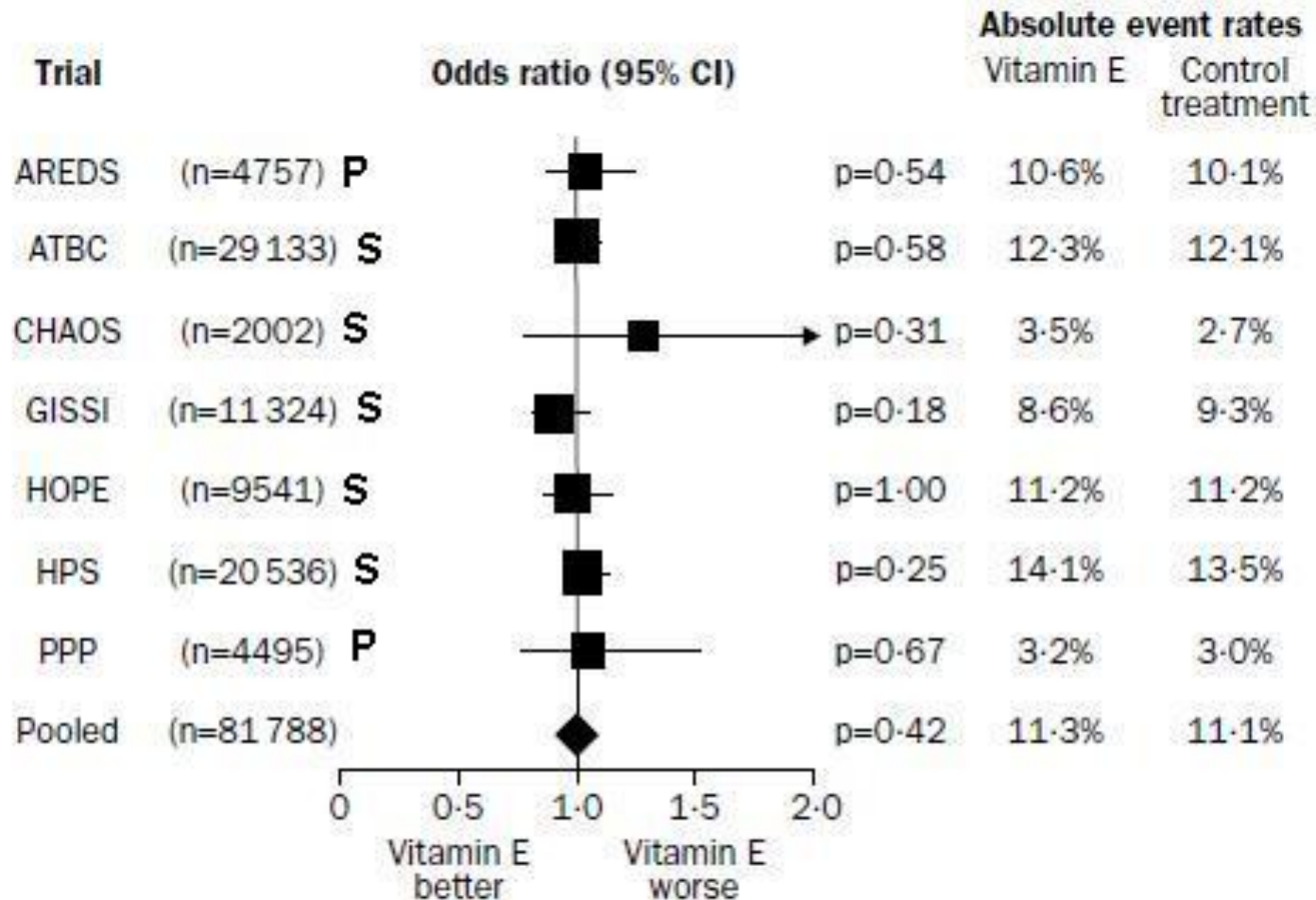
Breslow-Day test: $p=0.053$

Figure 7: Odds ratios (95% CI) of the combined endpoint of cardiovascular death or non-fatal MI for individuals treated with vitamin E or control therapy



No effect on mortality with vitamin E 300-800 U daily

Lancet 361:2017, 2003



Breslow-Day test: p=0.63

Figure 4: Odds ratios (95% CI) of all-cause mortality for individuals treated with vitamin E or control therapy



Heart Protection Lancet 360:23 2002

- 20536 adults with CAD, PAD, or DM
- Randomized placebo vs. 600 mg α vitamin E, 250 mg vitamin C, and 20 mg β carotene
- Total Mortality RR 1.04 (0.97 to 1.12)
- MI & CV death RR 1.02 (0.94 to 1.11)
- Stroke RR 0.99 (0.87 to 1.12)
- none significant



Not enough Vitamin E ?

Free Radic Biol Med 43:1388, 2007 (Roberts)

- Used natural Vitamin E (RRR-alpha-tocopherol)
- Significant reduction in oxidative stress was only seen at ≥ 1600 U daily
- No reduced oxidative stress until 16 weeks Rx
- Max dose in trials was 800 U (some trials used less effective Vitamin E)

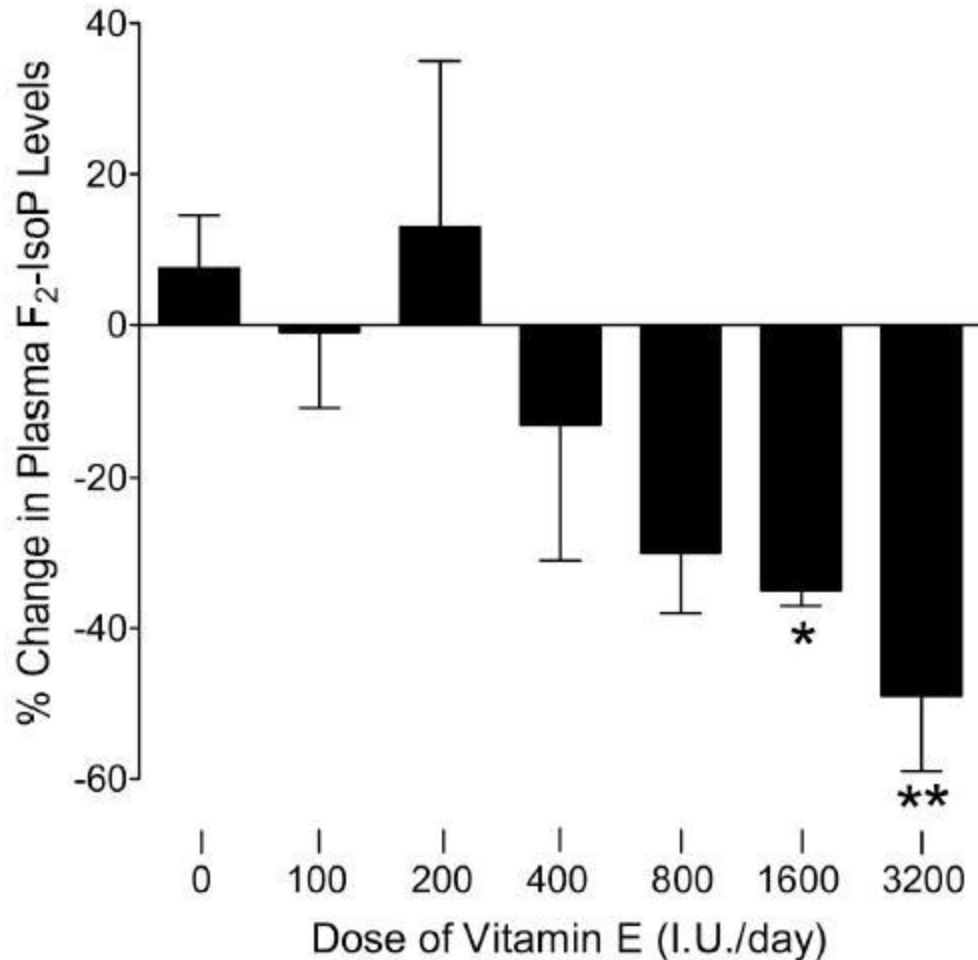


Figure 3. Relationship between the daily dosages of vitamin E administered for 16 weeks and suppression of plasma concentrations of F₂-isoprostanes (F₂-IsoPs). * $p < 0.03$ compared to placebo; ** $p < 0.005$ compared to placebo.



NASH CRN

Sanyal, et al, NEJM online 2010

- 247 adults with nonalcoholic steatohepatitis
- Randomized placebo, “natural” vitamin E 800 U, or pioglitazone 30 mg for 96 weeks
- **Vitamin E reduced histologic features of NASH** in 43% vs. 19% in placebo (p=0.001)
- Pioglitazone did not reduce histologic NASH - 43% of subjects vs. 19% placebo (p=0.04)
- Both Vitamin E and pioglitazone significantly reduced ALT (~20%) and AST by (~15%)

FAST – Probucol reduced CV events

and CIMT JACC 39:610, 2002



- 246 dyslipidemic patients randomized to placebo vs. probucol 500 mg vs. pravastatin 10 mg daily
- CIMT and CV Events (CV death, MI, revasc) at 2 years
- Significantly reduced CIMT and CV events

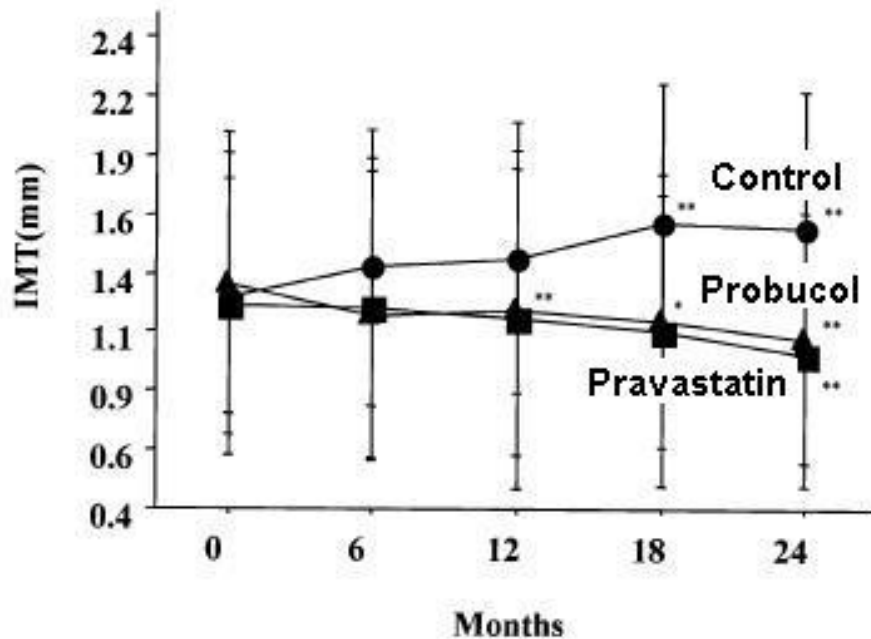


Figure 2. Changes in intima-media thickness (IMT) in the probucol (triangles), pravastatin (squares) and control (circles) groups. Data are presented as the mean value \pm SD. * $p < 0.05$; ** $p < 0.01$ vs. baseline.

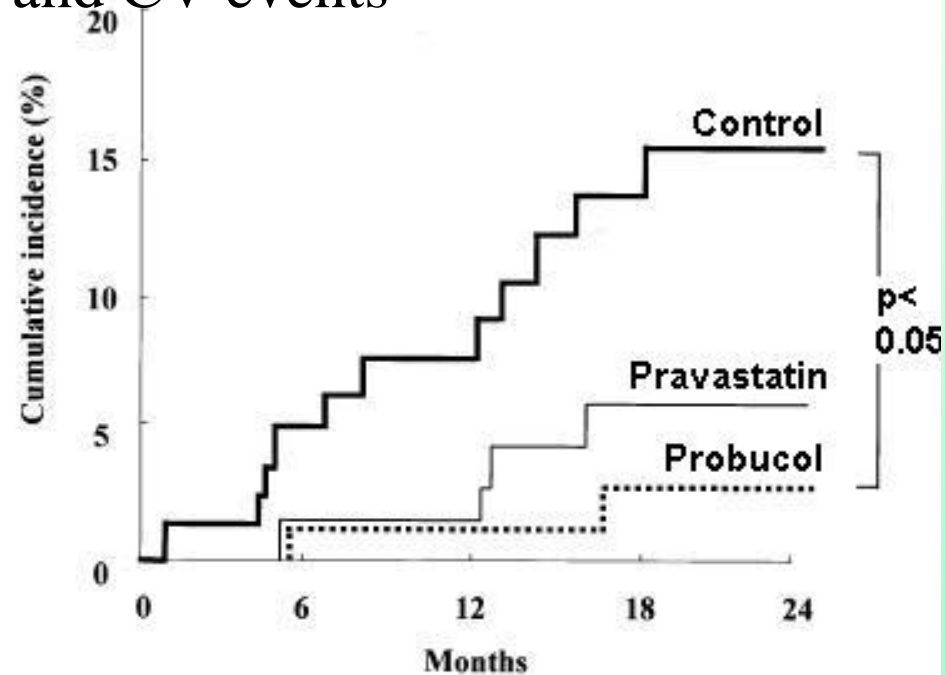


Figure 3. Kaplan-Meier estimates of the occurrence of all coronary events. **Bold solid line** = control group; **thin solid line** = pravastatin group; **broken line** = probucol group. There was a significant difference between the control group and probucol groups (* $p < 0.05$ by the log-rank test).



PQRST – No effect of probucol on femoral atherosclerosis AJC 74:875, 1994

- 274 patients with femoral atherosclerosis were randomized to placebo vs. probucol 500 mg
- Femoral IMT evaluated at 3 years
- No significant benefit

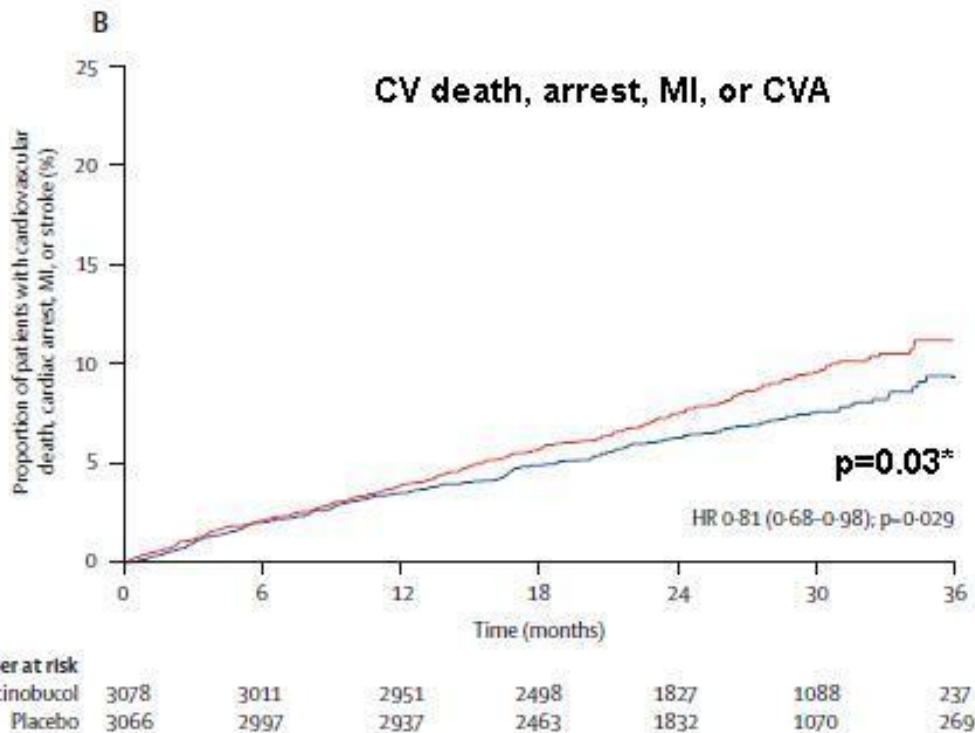
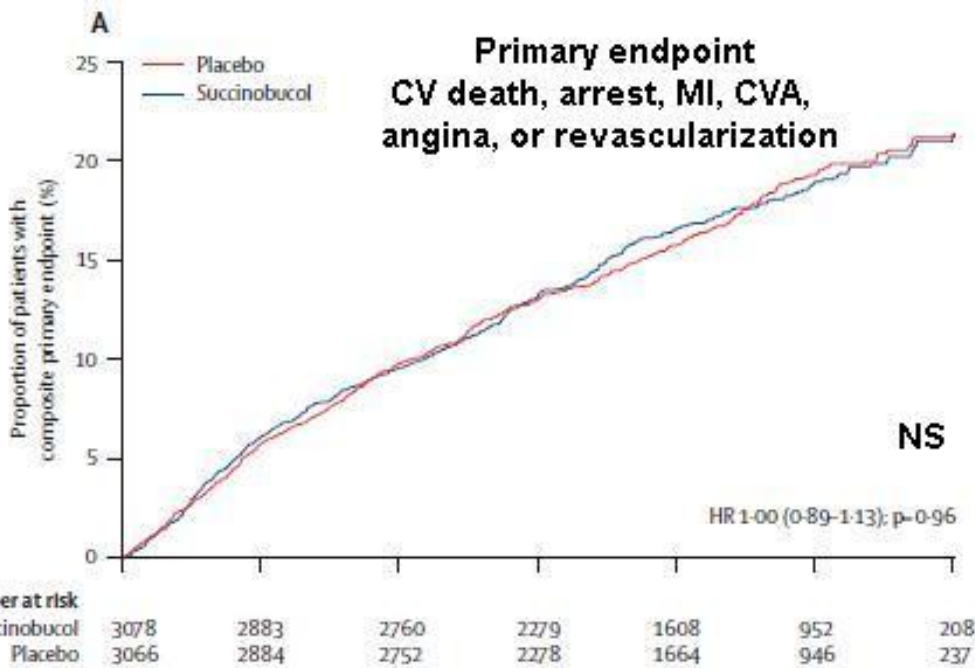
- Note that probucol increases QTc so it was removed from the US market



ARISE —

Succinobucol

Lancet 371:1761, 2008



- 6144 patients with acute coronary syndrome
- Randomized placebo vs. succinobucol 300 mg daily
- Significantly less CV death, arrest, MI, and CVA, but increased angina and revascularization that eliminated the benefit in the primary endpoint
- Not marketed



Lyon Diet Heart Study (1)

Circulation 99:779, 1999

- 605 patients <70 with ACS for 3.8 years
- Randomized (single blind) regular diet vs. Mediterranean diet (canola oil soft margarine)
- ASA 73%, β B 47%, ACEI 18%, Lipid 30%

	RRR	NNT
• Mortality	↓ 40%	18 (10 to -115)
• MI & CV death	↓ 68% *	10 (8 to 15)
• CV events	↓ 70% *	4 (4 to 5)
– MI/CV death/USAP/CHF/CVA/embolism		

Lyon Diet Heart Study (2)

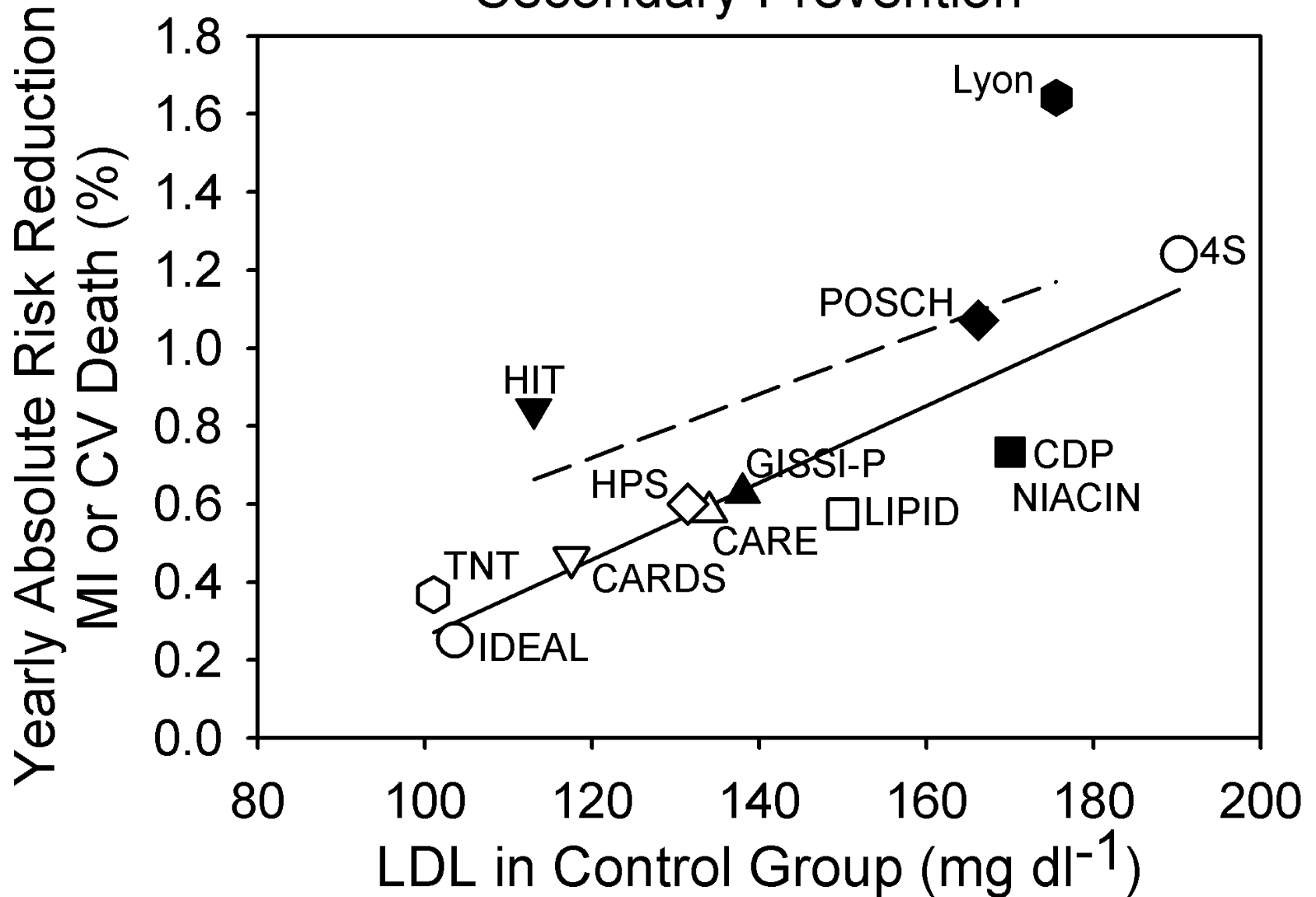


Circulation 99:779, 1999

	Control	Mediterranean	P
Lipids	33.6 %	30.4 %	0.002
Saturated	11.7 %	8.0 %	0.0001
Polyunsaturated	6.1 %	4.6 %	0.0001
18:1 Omega 9 (oleic)	10.8 %	12.9 %	0.0001
18:2 Omega 6 (linoleic)	5.3 %	3.6 %	0.0001
18:3 Omega 3 (linolenic)	0.3 %	0.8 %	0.0001
Calories	2088	1947	0.03
Protein	16.6	16.2	0.30
Cholesterol	312	203	0.0001
LDL	176	162	
HDL	45	48	

This effect is likely from omega 3 fats- ?antioxidants?

ARR with Statin vs. Non-Statin Trials Secondary Prevention



Antioxidants and CV disease



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- Beta carotene
 - No benefit
- Vitamin E
 - No benefit - dose appears to be low
- Probucol
 - Worked in one of two trial
- Succinobucol
 - Reduced MI/CVA - Increased angina/revasc