Translating Cardiovascular Nutrition from the Laboratory to the Clinic

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Effects of Bioactive Food Components Related to Cardiovascular Disease

- Lipoprotein metabolism
- Blood pressure
- Vascular reactivity
- Oxidative stress
- Inflammation
- Thrombosis

Food components that increase levels of atherogenic lipoproteins

- Cholesterol
- Most saturated fatty acids
- Trans-monounsaturated fatty acids

Bases for establishing effects of lipid-altering food components on CVD risk in humans

- Changes in lipoproteins (biomarkers) in animal models and humans
- Induction of atherosclerosis in animals (rodents, nonhuman primates)
- Mechanistic understanding of effects (cells, animals, humans)
- Observational studies of relationships between intake levels and CVD risk in human populations
- Randomized clinical trials of individual food components not feasible

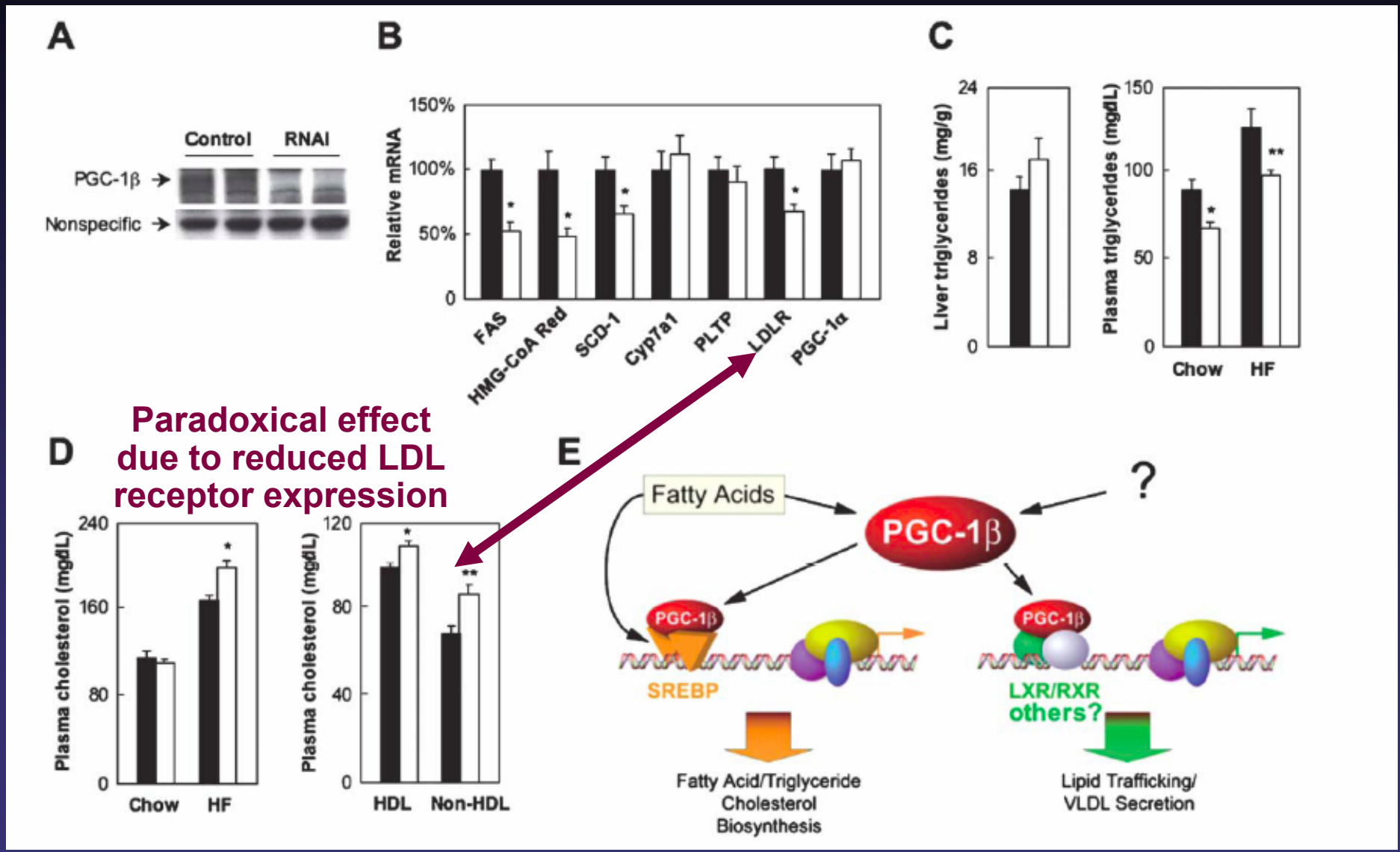
Cell, Vol. 120, 261–273, January 28, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.cell.2004.11.043

Hyperlipidemic Effects of Dietary Saturated Fats Mediated through PGC-1β Coactivation of SREBP

- Microarray analysis of gene expression in livers of mice fed saturated, polyunsaturated, and trans fatty acids:

  with sat and trans fat, PGC-1β mRNA increases along with SREBP1c, a major nuclear regulator of lipid synthesis genes
- PCC-1β is recruited to sterol response element of SREBP
- Viral expression of PGC-1β gene in vivo activates lipogenic genes and markedly increases hepatic lipoprotein secretion; the effect is dependent on SREBP and LXR
- Knockdown of PGC-1β by RNAi constructs in cultured cells: PGC-1βisrequired for full transcriptional activity of SREBP

In vivo knockdown of PGC-1β gene doesn't quite prove mechanism for saturated and trans fat-induced increases in plasma lipoproteins



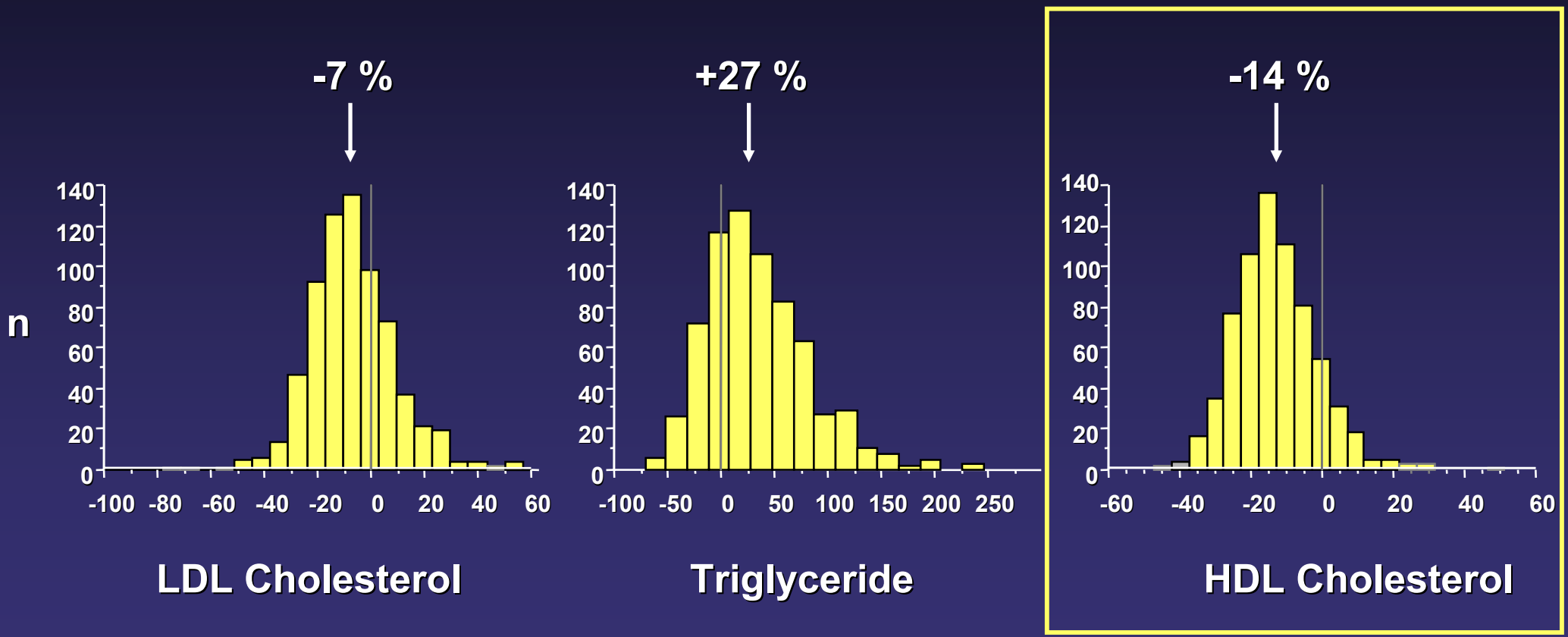
Lin et al., Cell 120:261, 2005

Factors limiting direct extrapolation from laboratory studies to clinic

- Differences in lipoprotein metabolism between animals and humans:
  - Mice, rats: HDL >> LDL; genetic manipulation does not reproduce all features of dietary regulation in humans
  - Rabbits: extreme dietary cholesterol responsiveness
  - Non human primates: generally lower triglycerides than humans
- Genetic variation among humans

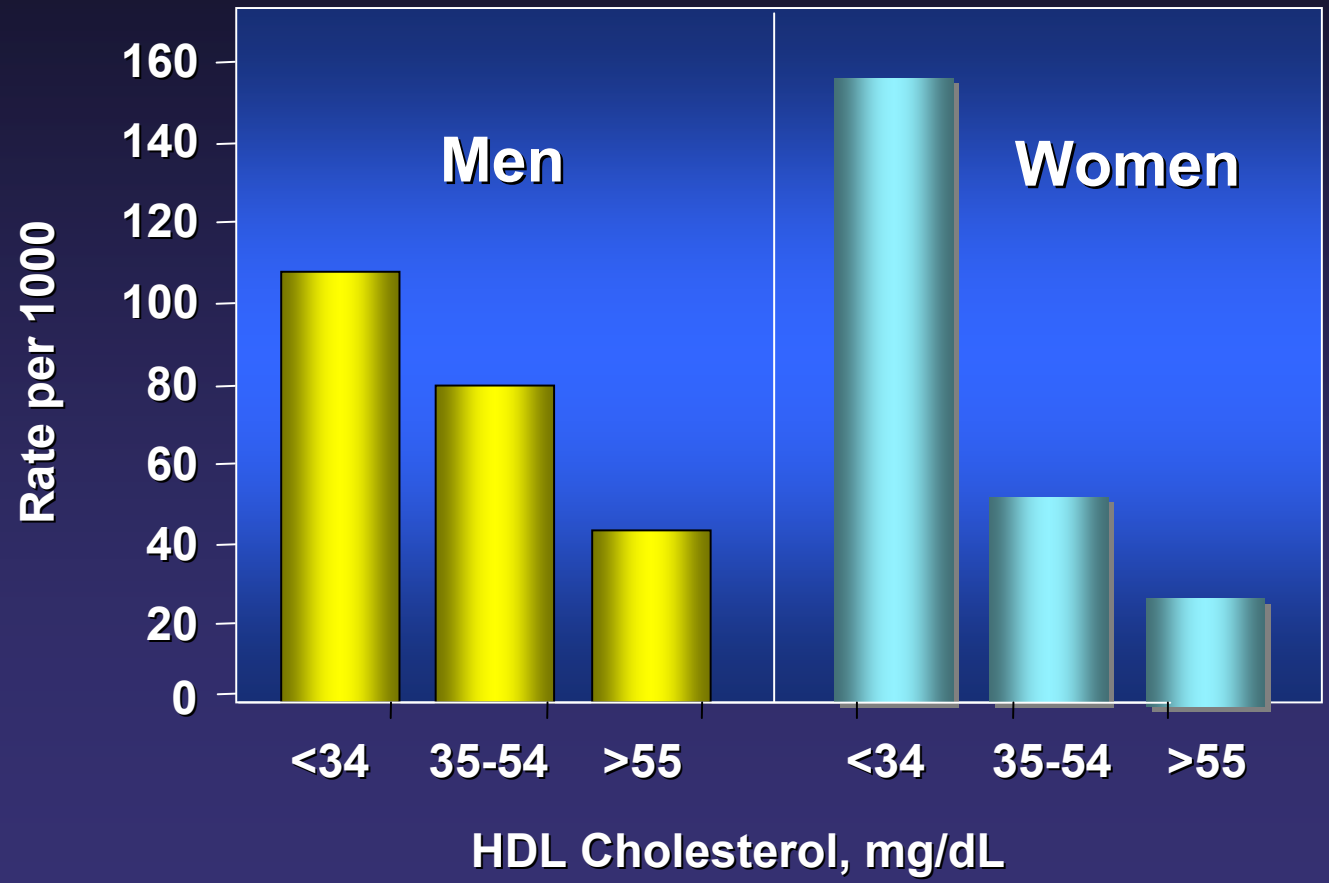
Distribution of Changes in Major Plasma Lipids with Low-Fat (20%) High-Carbohydrate (55%) Diet

n= 685 men and women



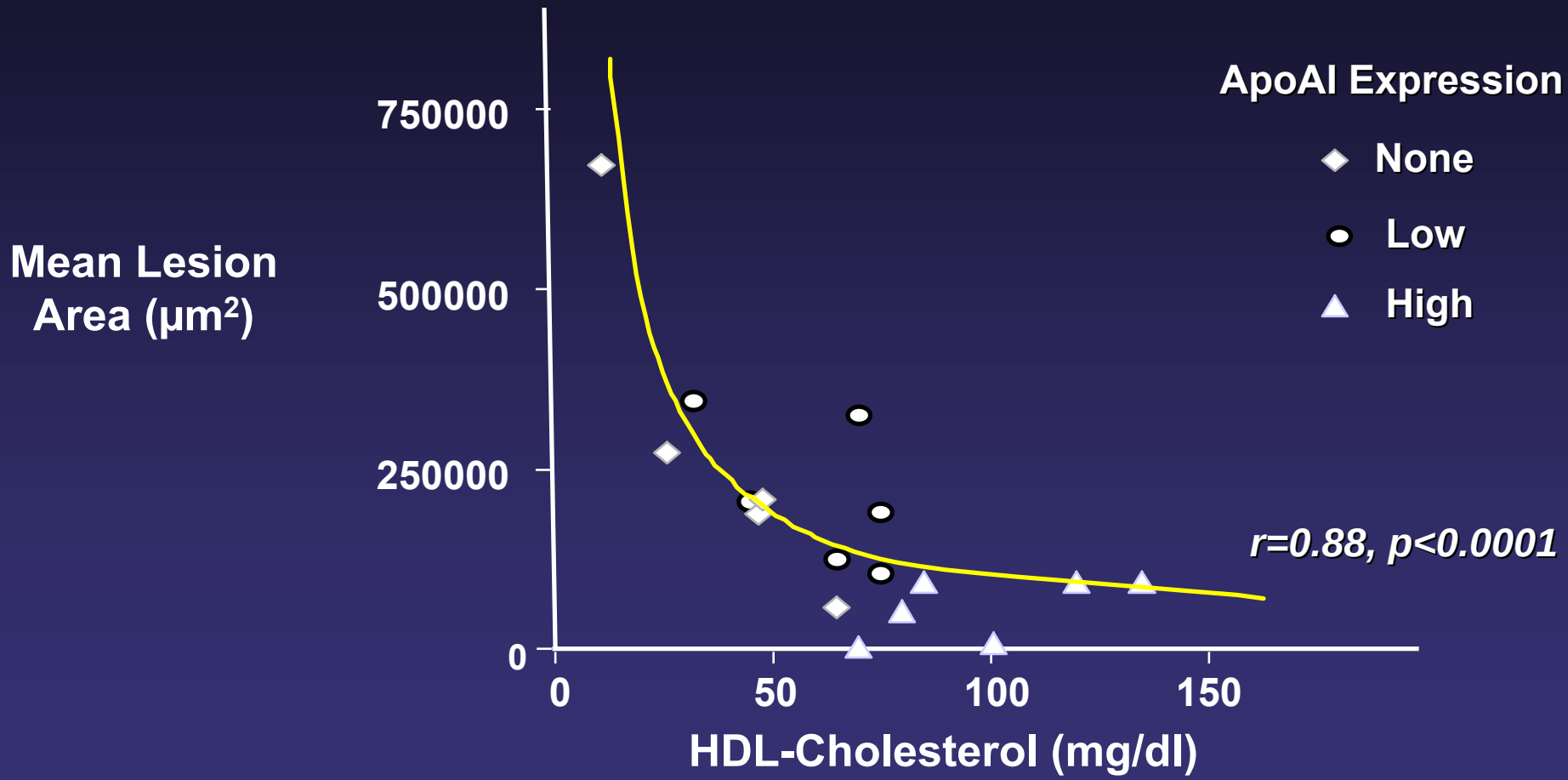
Percent change

Cardiovascular Disease and HDL-C Levels in the Framingham Study



Kannel WB. Am J Cardiol. 52:9B-12B, 1983

Relation of HDL-cholesterol to aortic atherosclerosis in apoE-deficient mice transgenic for human apoAI (model for increased apoAI transport)



Plump et al., PNAS 91:9607, 1994

What are the effects of dietary fatty acids on HDL in humans ?

Diet component	Effect on HDL		
Saturated fat	↑	Increases apoAI transport	Brinton et al., J Clin Invest 85:144, 1990
Polyunsaturated fat	↓	Increases apoAI catabolism	Brousseau et al., Athero-sclerosis 115:107, 1995
Trans-fat	↓	Increases apoAI catabolism	Matthan et al., ATVB 24:1092, 2004

What can we infer from these findings regarding expected effects of dietary fatty acids on CVD risk?

Other experimentally demonstrated bioactive properties of food components

- Polyphenols
  - Lower vascular reactivity, blood pressure, and thrombogenesis
  - Nutritional epidemiology supportive
- Omega-3 fatty acids
  - Improve cardiac electrophysiology, thrombosis, inflammation
  - Epidemiology and clinical trial evidence supportive

Antioxidants - A Case Study

Involvement of oxidative stress in atherosclerosis

- Oxidative modification of atherogenic lipoproteins is critical for arterial macrophage lipid uptake and formation of foam cells and fatty streaks
- Oxidized lipids are proinflammatory and promote endothelial dysfunction, plaque destabilization, and thrombosis
- Oxidation markers are present in atherosclerotic lesions of animal models, e.g., hyperlipidemic apoE knockout
- Vitamin E deficiency induced by knockout of α-tocopherol binding protein in hyperlipemic mice increases atherosclerosis
- Targeted disruption of 12/15 lipoxygenase reduces atherosclerosis

Antioxidants - A Case Study

Dietary antioxidants and atherosclerosis in animal models

- Vitamin E supplementation in vivo reduces lipoprotein oxidation in vitro
- Dietary antioxidants reduce atherosclerosis in some animal models

Antioxidants - A Case Study

Evidence for reduction of CVD risk in humans

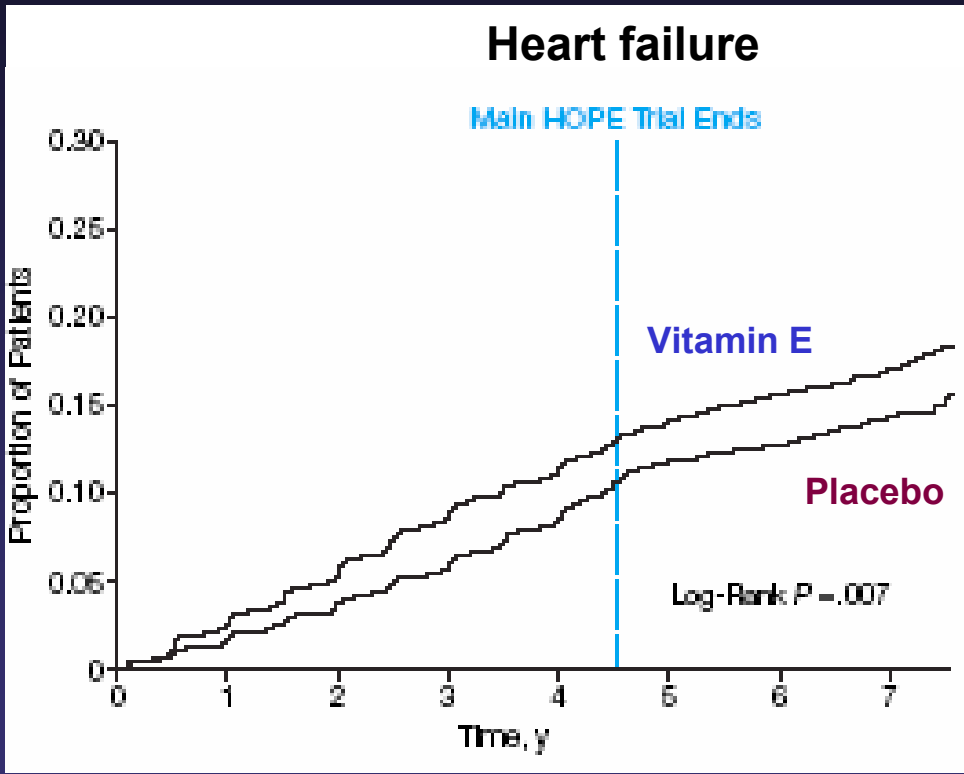
- Observational studies
  - Relative risk reduction associated with high vitamin E intake ~30-65%
  - Reduced plasma antioxidant levels associated with CHD
  - Dietary antioxidant-disease relationships confounded by other health-related behaviors
- Randomized clinical trials

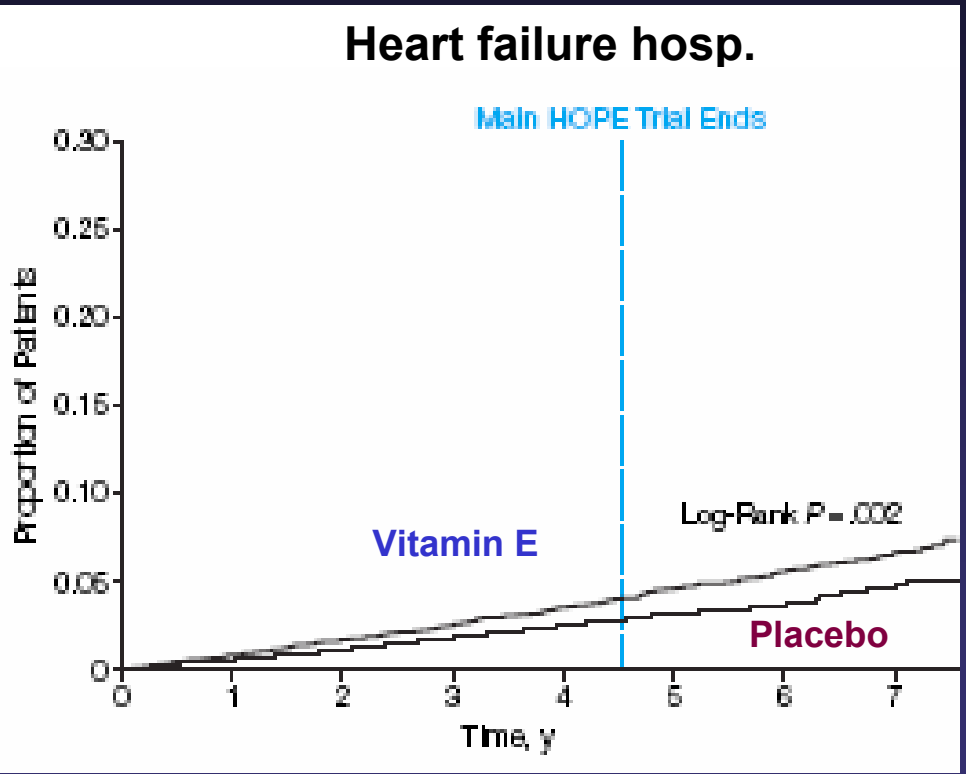
Summary of Randomized Controlled Trials of Antioxidant Vitamin Supplementation in CVD

Trial	n	Dose (daily)	Follow up(yrs)	Relative Risk(95% CI) 1° CVD Outcome	CVD Mortality
CHAOS	2,002	E-800/400	1.4	0.53 (0.34-0.83)*	1.18 (0.62-2.27)
GISSI	11,324	E-300 IU	3.5	0.95 (0.86-1.05)	1.00 (0.88-1.14)
HOPE	9,541	E-400 IU	4.5	1.05 (0.95-1.15)	1.05 (0.90-1.22)
SPACE	196	E-800 IU	1.4	0.54 (0.33-0.89)*	0.61 (0.28-1.30)
PPP	4,495	E-300 IU	3.6	1.07 (0.74-1.56)	0.86 (0.49-1.52)
HPS	20,536	E-600 IU+ C-250 mg+ β-carotene-20 mg	5	1.02 (0.94-1.11)	1.05 (0.95-1.15)

*Significant

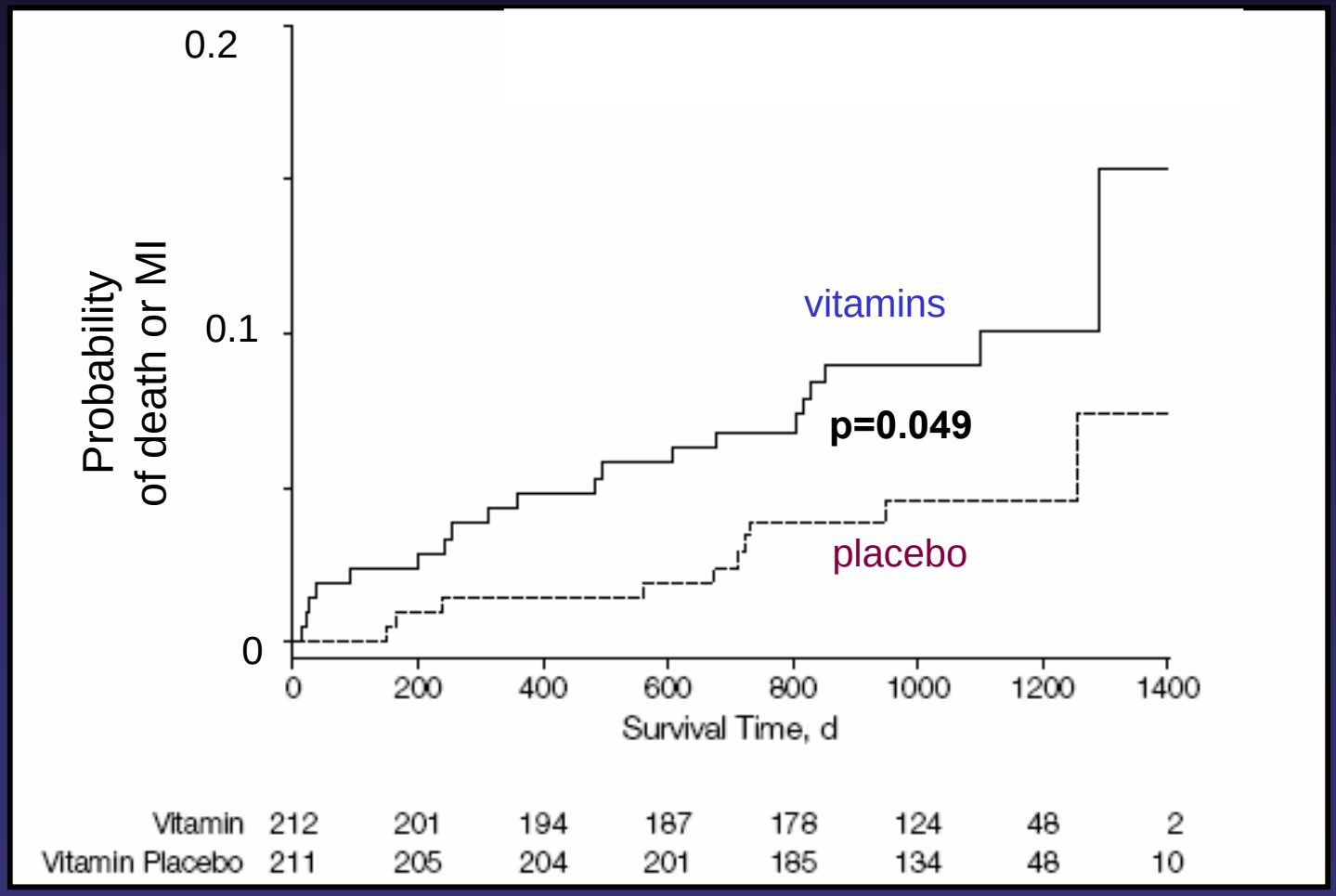
HOPE Trial: Increased risk for heart failure in patients with CVD or diabetes treated with 400 IU vitamin E





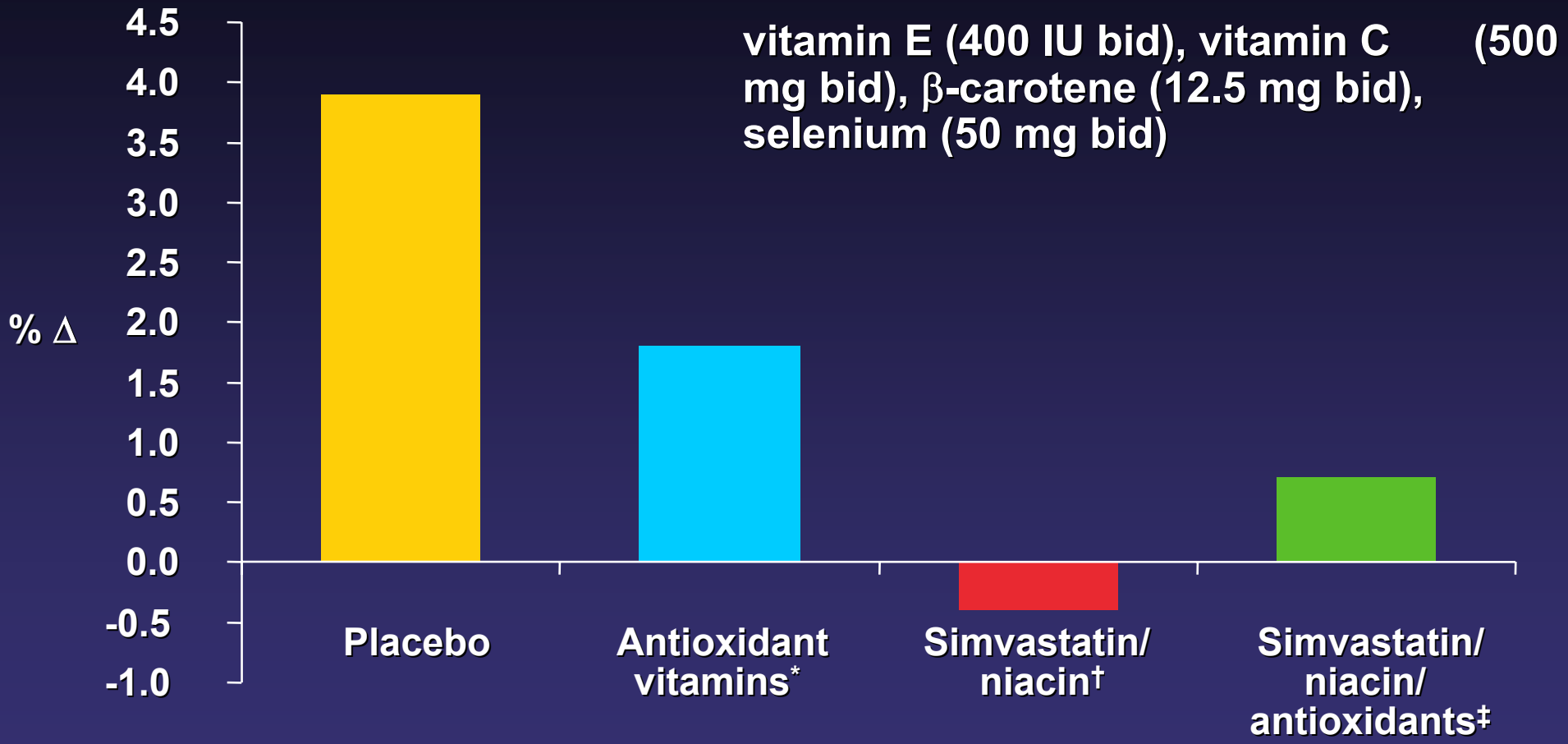
JAMA 293:1338, 2005

WAVE Trial: Probability of death or nonfatal MI with vitamin E 400 IU bid and vitamin C 500 mg bid in postmenopausal women



Waters et al., JAMA 288:2432, 2002

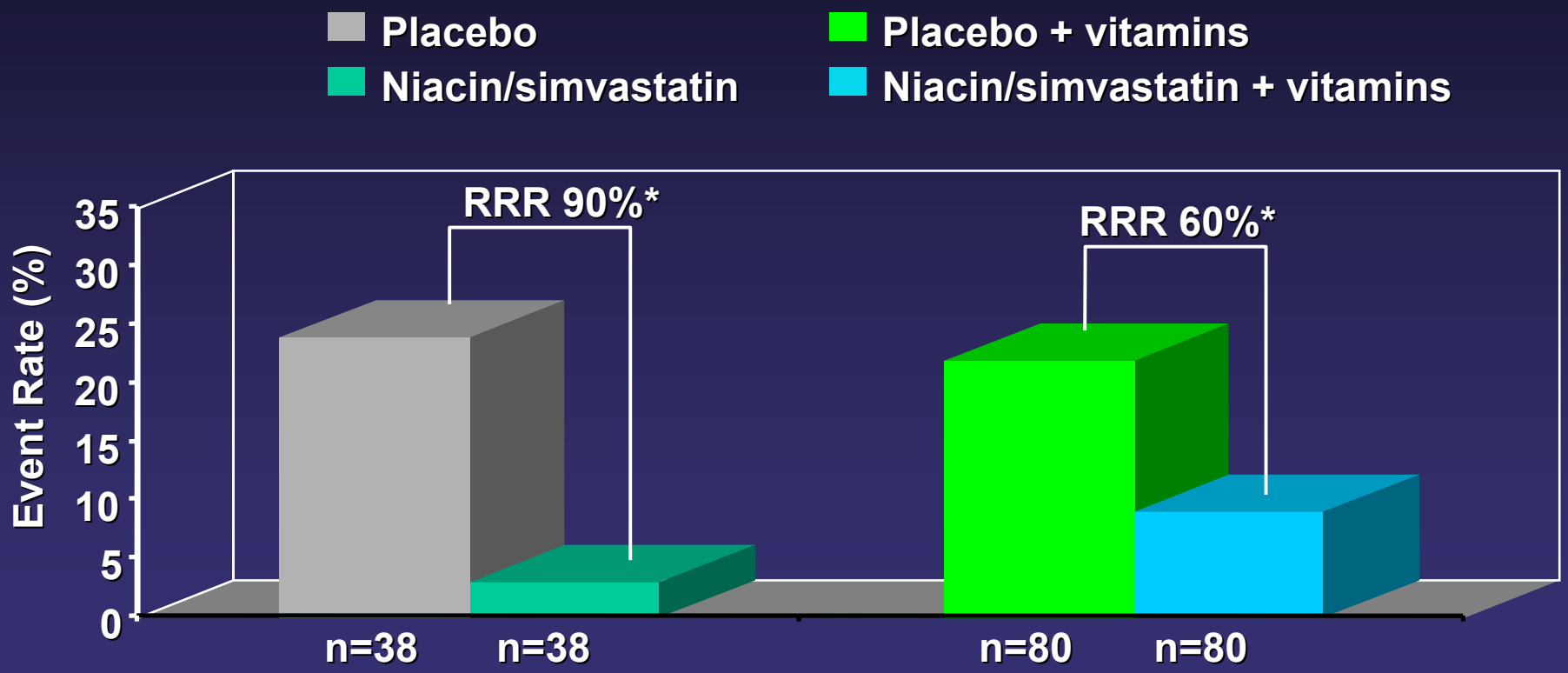
HATS: Percent change in coronary artery stenosis with lipid lowering drugs and/or antioxidants



*p=0.16 for comparison with placebo; †p<0.001; ‡p=0.004.
HATS=HDL-Atherosclerosis Treatment Study.

Brown et al. N Engl J Med. 345:1583, 2001

HATS: Clinical events with lipid lowering and/or antioxidants



*$P<0.01$

Brown et al. N Engl J Med. 345:1583, 2001

VEAPS: Effects of vitamin E on early carotid artery atherosclerosis (intimal-medial thickness)

IMT progression rate, mm/y	Placebo (n=170)	Vitamin E (n=162)	p
All evaluable subjects	0.0023±0.0007	0.0040±0.0007	0.08
Adjusted for baseline LDL	0.0024±0.0007	0.0039±0.0007	0.13
Females (n=87/85)	0.0026±0.0009	0.0036±0.0009	0.40
Males (n=83/77)	0.0020±0.0010	0.0044±0.0011	0.11

Hodis et al. Circulation 106:1453, 2002

Antioxidants - A Case Study

- Despite strong evidence supporting benefits of antioxidants in cellular and animal studies, trials of dietary antioxidants in humans have largely failed to confirm benefits on CVD, and in some cases have suggested harm.
- If dietary antioxidants have potential for CVD prevention, more studies are needed to determine optimal levels and combinations, appropriate subgroups for treatment, and suitable model systems that better predict outcomes in humans.

Conclusions

While basic research in model systems will continue to be of critical importance in understanding nutritional effects on CVD, increasing efforts should be made to promote the development and application of improved molecular and clinical approaches for directly assessing relevance of these effects in humans.