Vitamin Supplements and Cardiovascular Disease

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Funded by National Institute on Aging
R01-AG13860 and R01-AG17160
and
Office of Dietary Supplements

Reduction in Coronary Events in Major LDL-C Lowering Clinical Trials

Study	Risk Reduction (N) Overall	Men	Women	Baseline LDL
Secondary Prevention				
4S[1]	34% (4444)	34% (3617)	35% (827)	188 mg/dL
CARE[2]	24% (4159)	20% (3577)	45% (582)	139 mg/dL
LIPID[3]	24% (9014)	26% (7498)	11% (1516)	150 mg/dL
Primary Prevention				
WOS[4]	31% (6595)	31% (6595)	n/a	192 mg/dL
Afcaps[5]	36% (6605)	37% (5608)	46% (997)	150 mg/dL

[1]Lancet 1994;344:1383-1389. [2]N Engl J Med 1996;335:1001-1009. [3]N Engl J Med 1998;339:1349-1357.
[4]N Engl J Med 1995;333:1301-1307. [5] JAMA 1998;279:1615-1622.

Therapies Beyond LDL-C

- Triglyceride-rich lipoprotein reduction
- HDL-C elevation
- Hormone replacement therapy
- Antioxidant vitamin supplementation
- Homocysteine reduction
- Infection/Inflammation
- Lp(a) reduction
- ApoC-III
- Fibrinogen

Epidemiological Studies – Antioxidant Vitamins

	Vitamin E	Vitamin C	ß-carotene
NHS	0.54 (0.36-0.82)	0.80 (0.58-1.10)	0.78 (0.59-1.03)
	Nonfatal MI or coronary death		
IWHS	0.38 (0.18-0.80)-diet	1.43 (0.75-2.70)	1.19 (0.67-2.12)
	CHD death		
HPFS	0.70 (0.55-0.89)	1.25 (0.91-1.71)	0.71 (0.53-0.86)
	Nonfatal MI, coronary death or revascularization		
FMC:men	0.68 (0.42-1.11)	1.00 (0.68-1.45)	1.02 (0.70-1.48)
	CHD death		
FMC:women	0.35 (0.14-0.88)	0.49 (0.24-0.98)	0.62 (0.30-1.29)
	CHD death		
Vitamin C			
BDHSSS	0.80 (0.60-1.30)	CVD death	
WES	0.75 (0.52-1.07)	CHD death	
ACS	1.01	Circulatory disease death	
NHANES	0.66 (0.53-0.82)	CVD death	
ß-carotene			
WES	0.84	CHD death	
MHCPS	0.54 (0.34-0.86)	CVD death	

Summary of Antioxidant Vitamin Supplementation Randomized Controlled Event Trials of CVD

Trial	N	Supplement (daily)	Follow-up (years)	Relative Risk(95% CI) Primary CVD Outcome	Relative Risk(95% CI) CVD Mortality
CHAOS	2,002	E-800/400 IU	1.39	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	1.42	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+ ß-carotene-20 mg	5	1.02(0.94-1.11)	1.05(0.95-1.15)

*Signficant

Summary of Antioxidant Vitamin Supplementation 2x2 Randomized Controlled Trials of CVD

Trial	N	Follow-up (years)	Treatment	Relative Risk(95% CI) CVD Outcome
GISSI	11,324	3.5	E-300 IU	0.95(0.86-1.05)
			n-3 PUFA	0.90(0.82-0.99)
HOPE	9,541	4.5	E-400 IU	1.05(0.95-1.15)
			ACE inhibitor	0.78(0.70-0.86)
PPP	4,495	3.6	E-300 IU	0.94(0.77-1.16)
			Aspirin	0.77(0.62-0.95)
HPS	20,536	5	E-600 IU+C-250 mg +B-carotene-20 mg	1.02(0.94-1.11)
			Statin	0.83(0.75-0.91)

Summary of Antioxidant Vitamin Supplementation Randomized Controlled Atherosclerosis Imaging Trials

4 RCT's with atherosclerosis progression as the primary outcome

Carotid intima-media thickness by B-mode ultrasonography

Antioxidant Supplementation in Atherosclerosis Prevention Study (ASAP)
J Int Med 2000;248:377-386

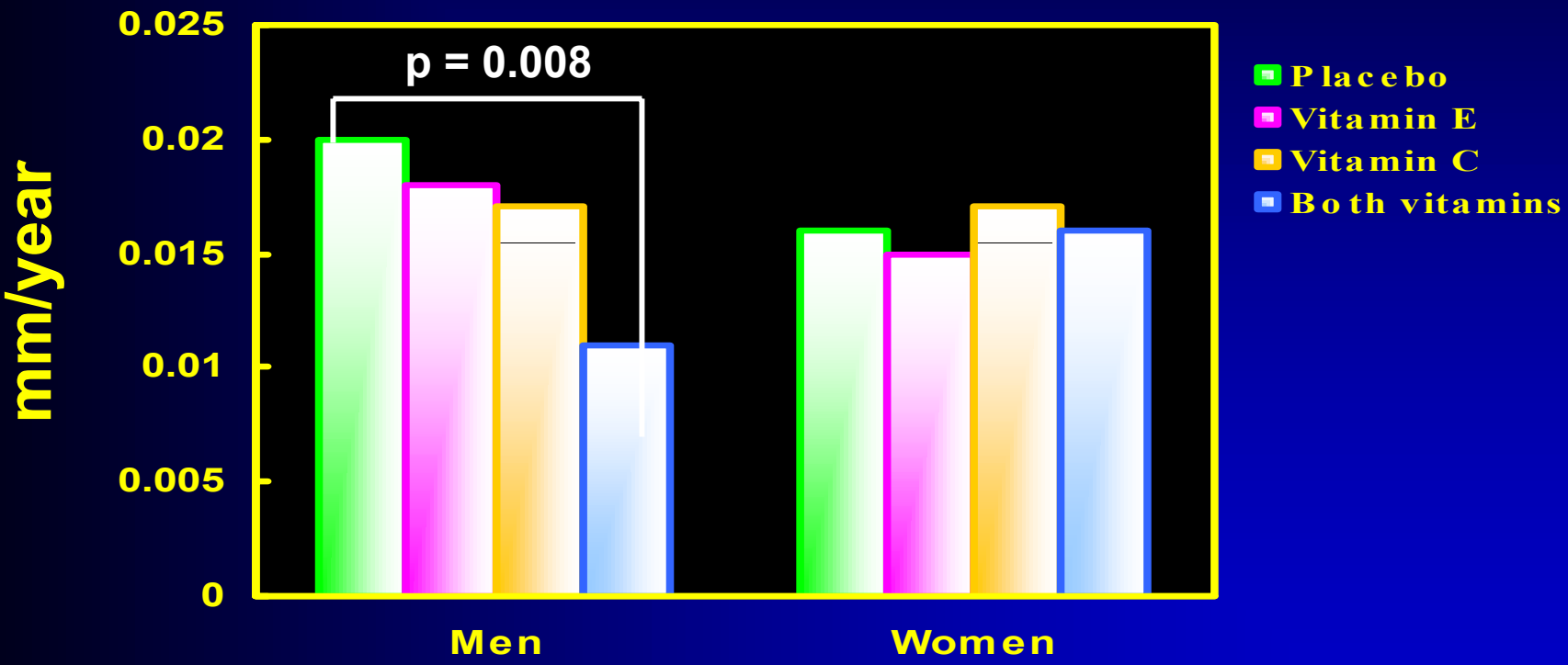
Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E (SECURE)
Circulation 2001;103:919-925

Coronary artery disease by quantitative coronary angiography

HDL Atherosclerosis Treatment Study (HATS)
N Engl J Med 2001;345;1583-1595

Women's Angiographic Vitamin and Estrogen Trial (WAVE)
JAMA 2002;288;2432-2440

Antioxidant Supplementation in Atherosclerosis Prevention Study (ASAP)



Summary of Randomized Controlled Trials - Vitamin E

Whether vitamin E supplementation reduces the progression of subclinical atherosclerosis in a healthy cohort of men and women at low-risk for CVD remains untested

Vitamin E Atherosclerosis Prevention Study (VEAPS)

Study Design:	randomized, double-blind, placebo-controlled trial
Subjects:	353 healthy men and women ≥40 years old without preexisting CVD
Intervention:	400 IU/day of synthetic DL-α-tocopherol placebo
Follow-up:	3 years
1º outcome:	rate of change of the right distal far wall CCA IMT in computer image processed B-mode ultrasonograms obtained every 6 months

Hodis, et al. Circulation 2002;106:1453-1459.

VEAPS

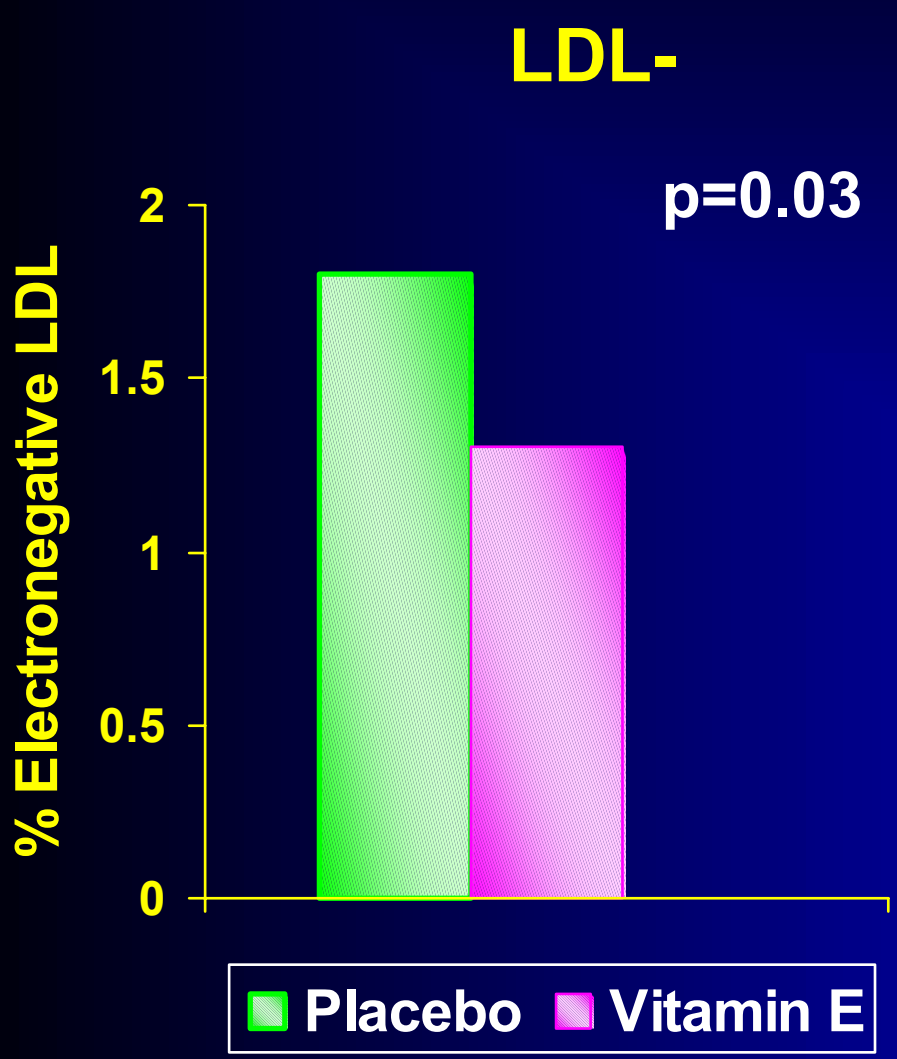
Plasma Vitmain E Levels (μmol/L)

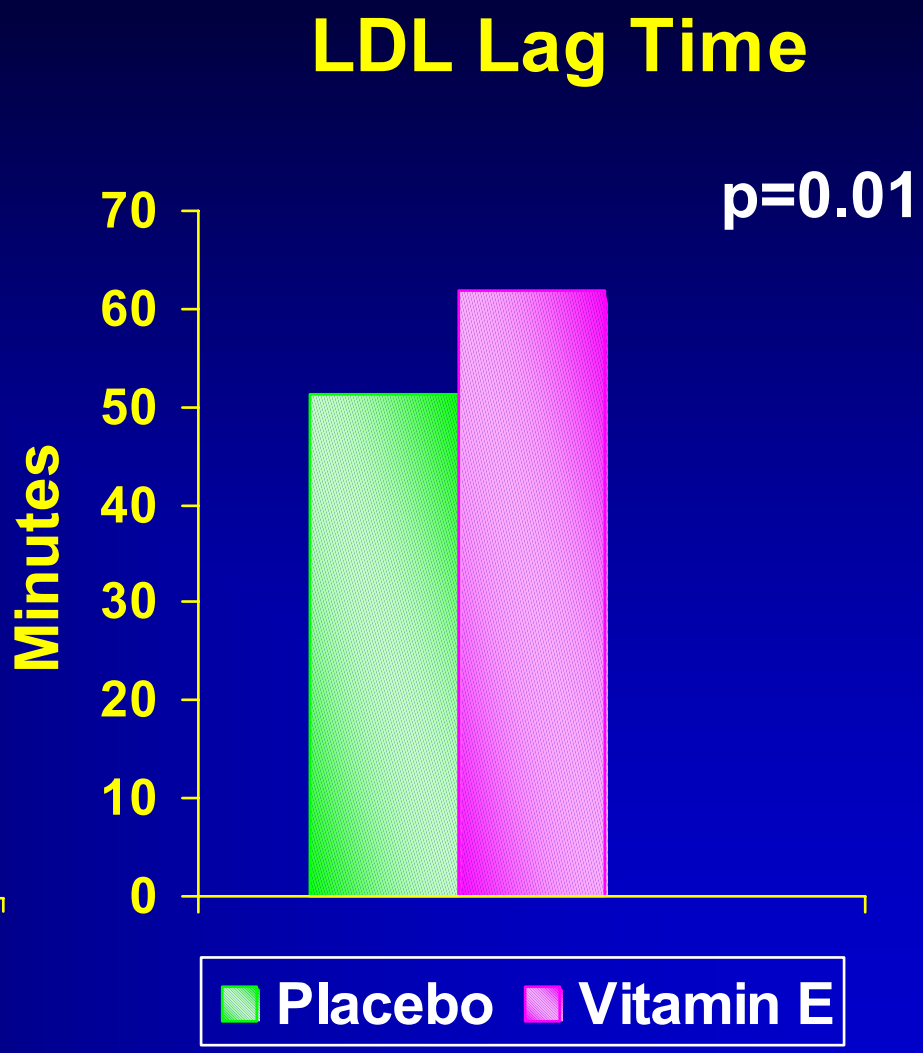
	Placebo (n = 170)	Vitamin E (n = 162)	p-value
Baseline	23.2±6.3	22.1±6.3	0.16
On-trial	30.9±6.2	53.3±12.7	<0.0001
p-value	<0.0001	<0.0001	

Hodis, et al. Circulation 2002;106:1453-1459.

VEAPS

Effect of Vitamin E on LDL Oxidation in VEAPS

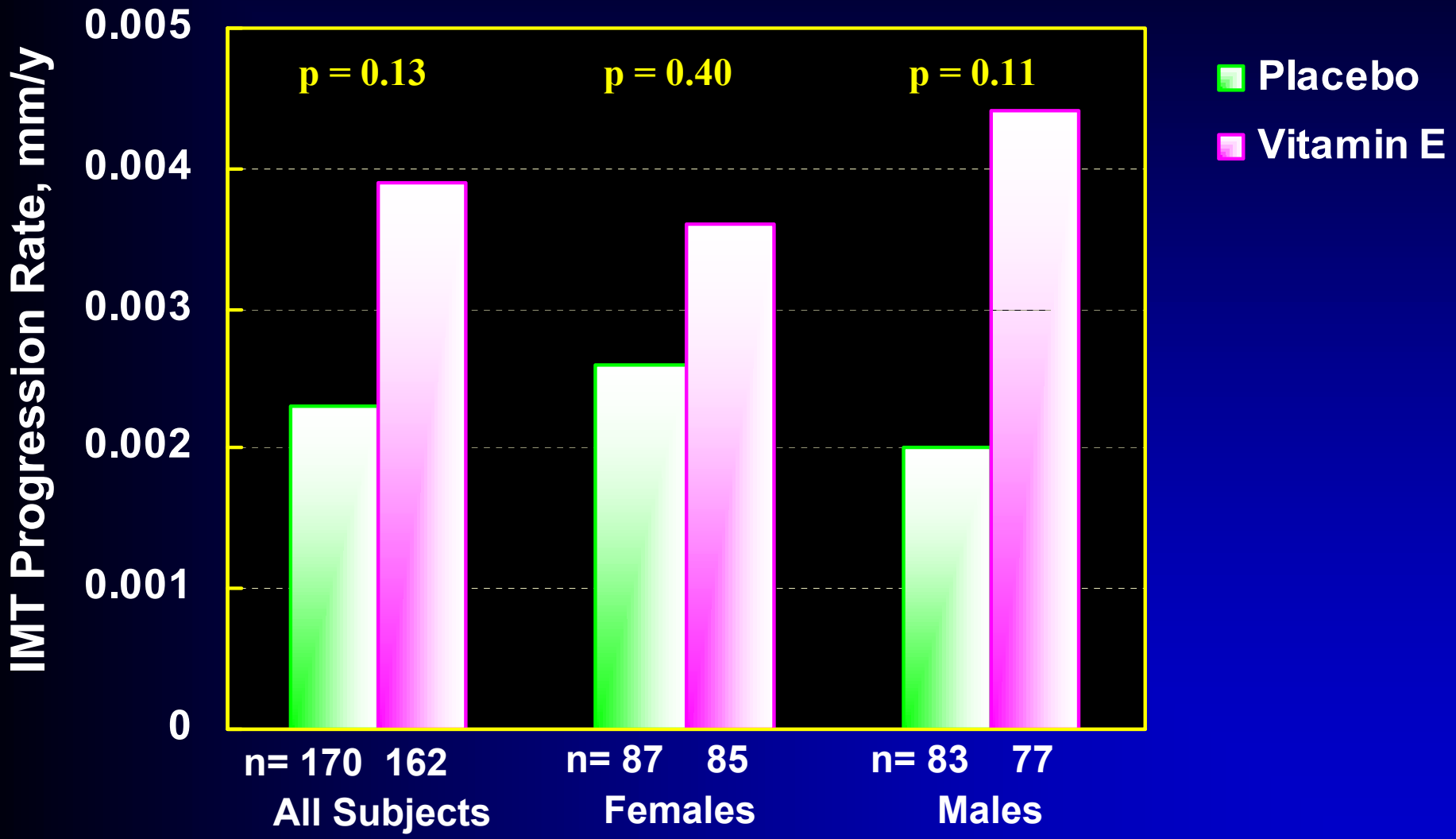




Hodis, et al. Circulation 2002;106:1453-1459.

VEAPS

VEAPS Primary Trial Results



Hodis, et al. Circulation 2002;106:1453-1459.

VEAPS

Summary

- Supplementation with DL-α-tocopherol significantly raised plasma vitamin E levels and reduced LDL^- and LDL oxidative susceptibility relative to placebo.
- However, vitamin E supplementation did not reduce the progression of CCA IMT over a 3-year period, overall and stratified by sex.
- Clinically significant side-effects were not observed.

Hodis, et al. Circulation 2002;106:1453-1459.

VEAPS

Conclusion

- Use of vitamin E in primary or secondary prevention of CVD for the general population at large is not currently supported by RCT's.
- VEAPS indicates that in well-nourished healthy vitamin E replete individuals at low risk for CVD, vitamin E supplementation has no perceptible effect on the progression of atherosclerosis.
- However, the data indicate that special populations, perhaps those with low serum antioxidant vitamin levels may derive CVD benefit from antioxidant vitamin supplementation.

Hodis, et al. Circulation 2002;106:1453-1459.

VEAPS

Therapies Beyond LDL-C

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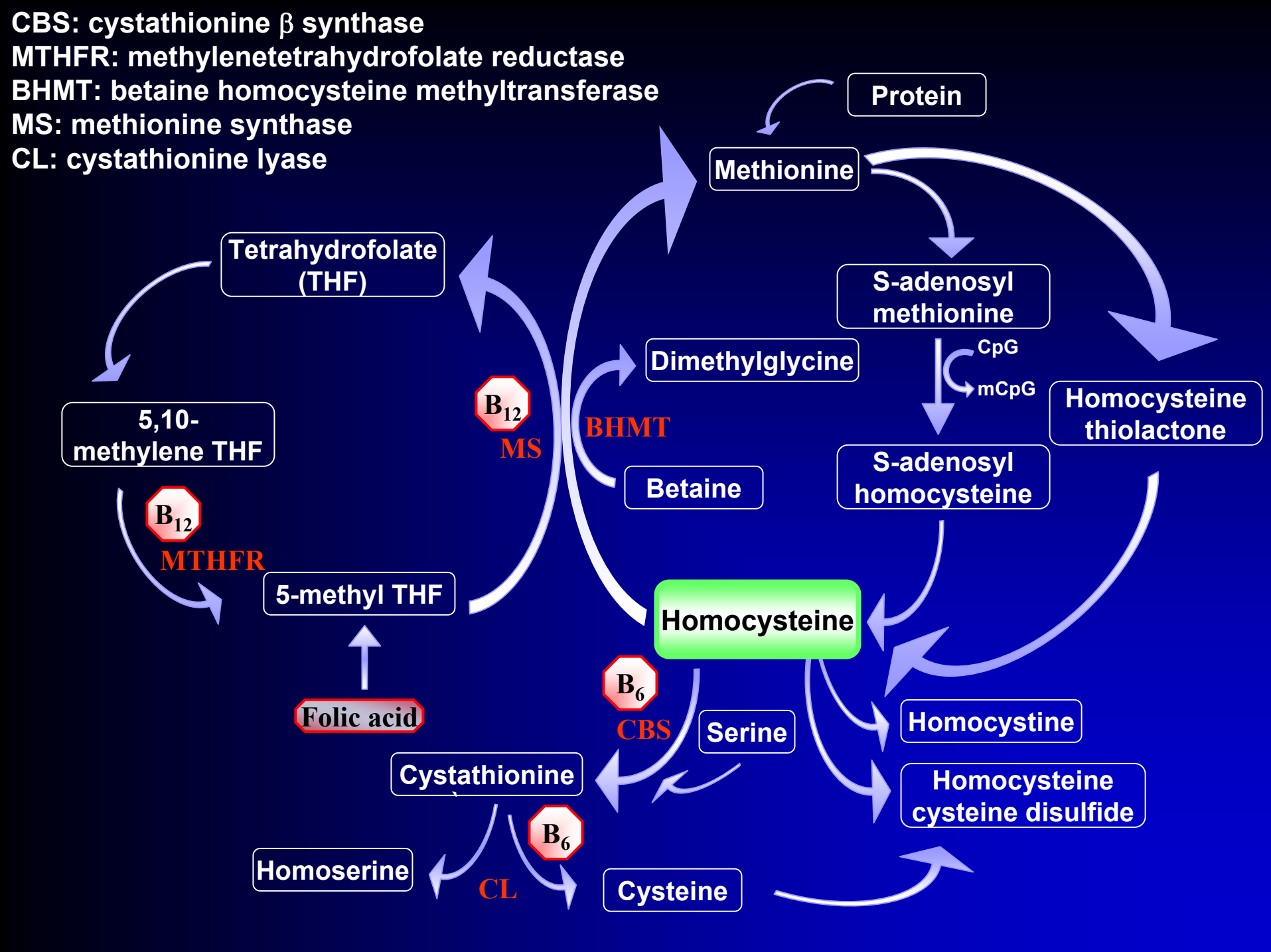
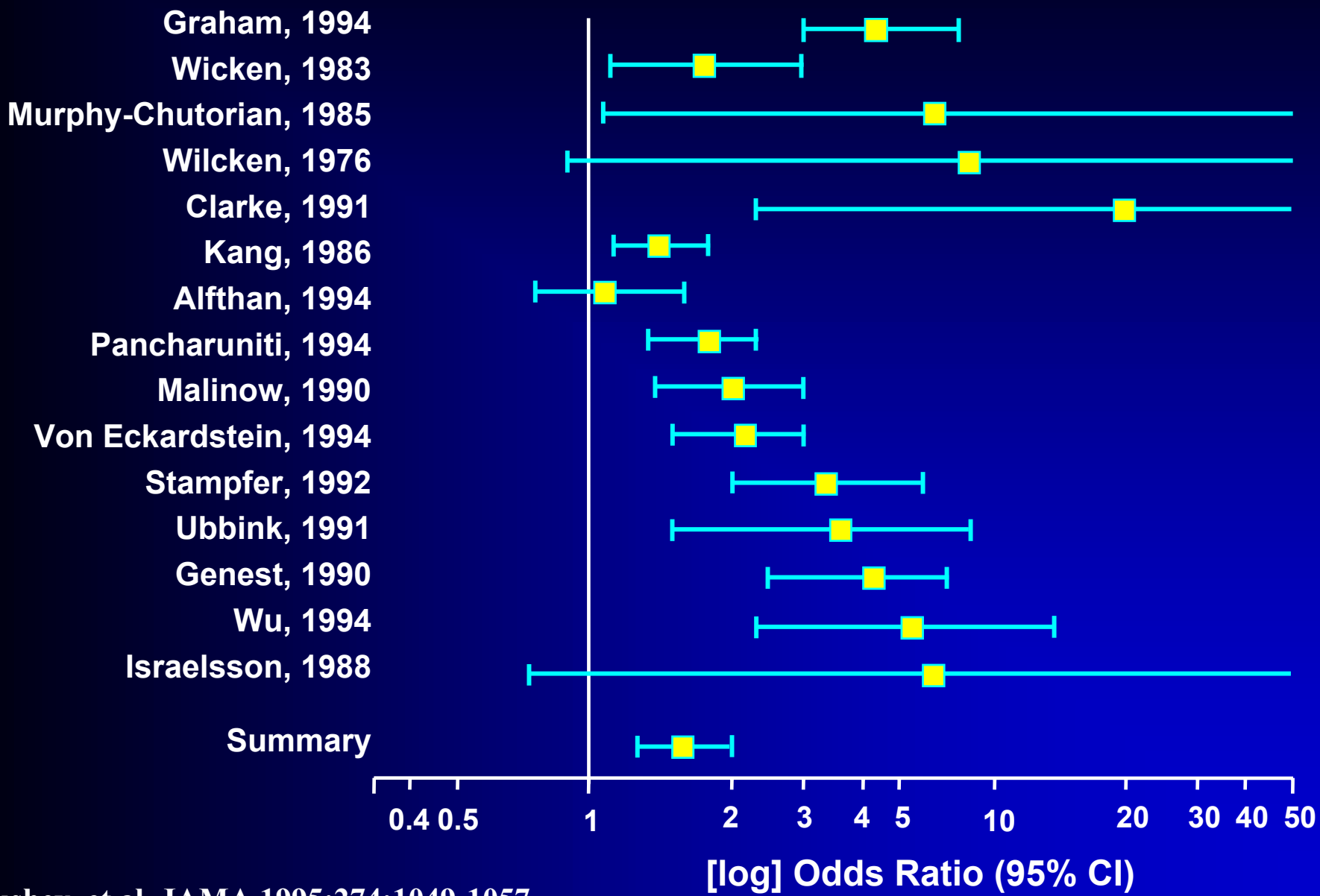
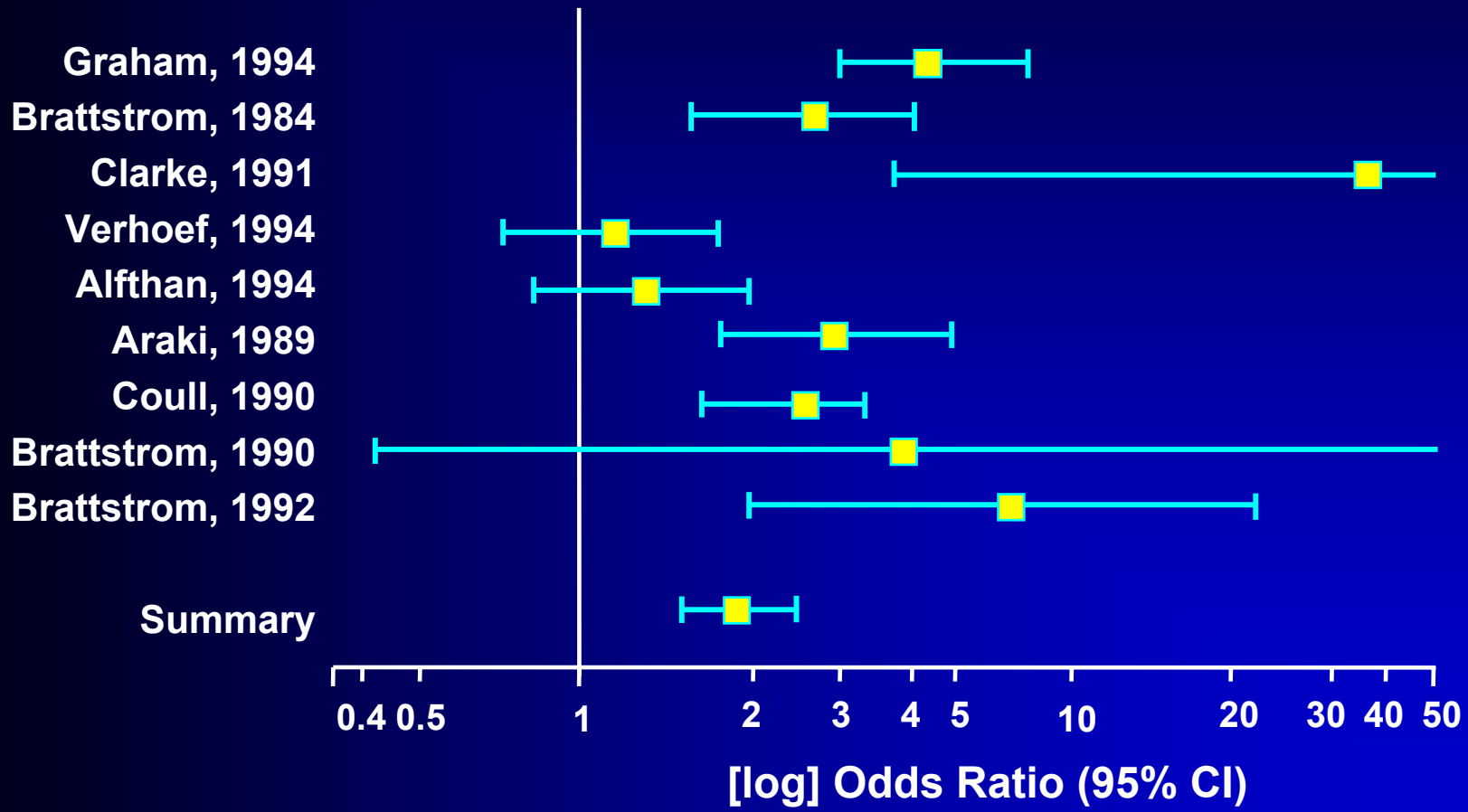

CBS: cystathionine β synthase
MTHFR: methylenetetrahydrofolate reductase
BHMT: betaine homocysteine methyltransferase
MS: methionine synthase
CL: cystathionine lyase
Protein
Methionine
Tetrahydrofolate (THF)
S-adenosyl methionine
CpG
mCpG
Dimethylglycine
Homocysteine thiolactone
5,10-methylene THF
B12
MS
BHMT
Betaine
S-adenosyl homocysteine
B12
MTHFR
5-methyl THF
Homocysteine
Folic acid
B6
CBS
Serine
Homocystine
Cystathionine
Homocysteine cysteine disulfide
B6
Homoserine
CL
Cysteine

Homocysteine and CHD



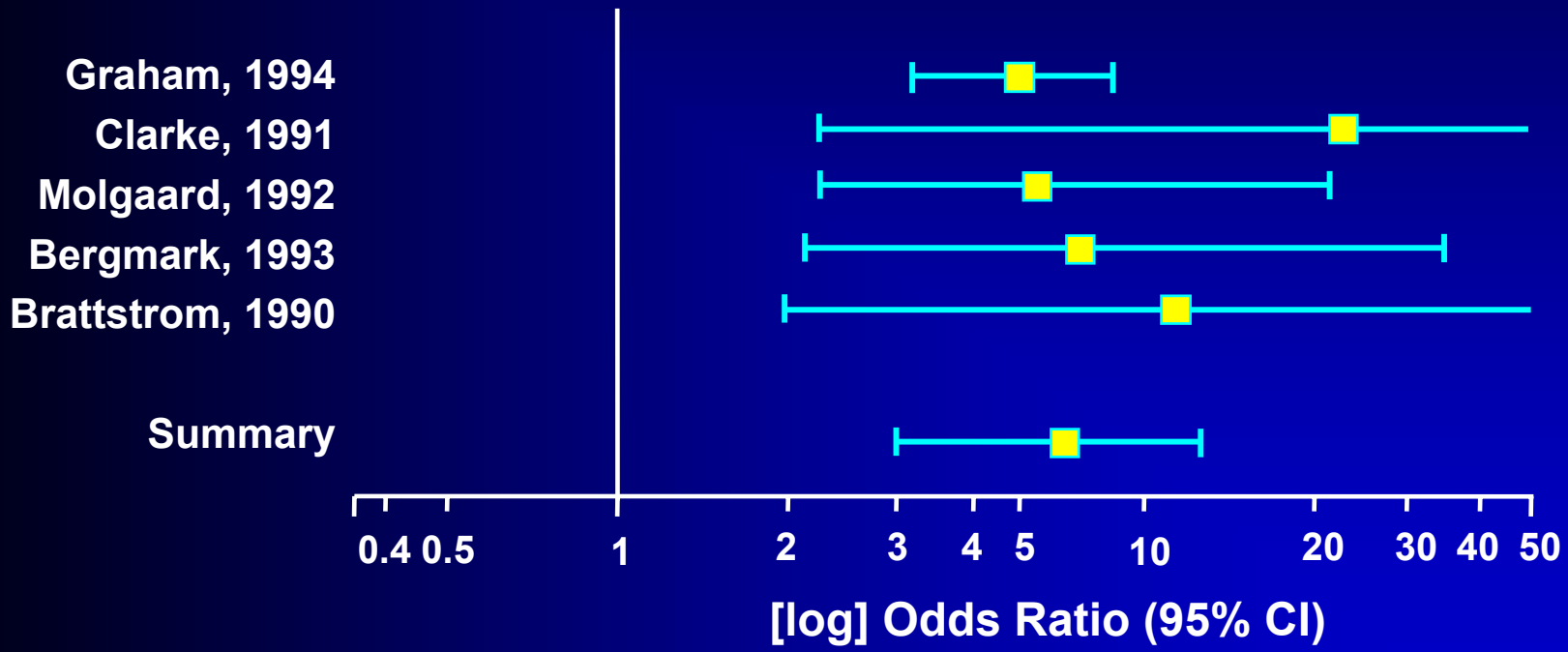
Boushey, et al. JAMA 1995;274:1049-1057.

Homocysteine and Cerebrovascular Disease



Boushey, et al. JAMA 1995;274:1049-1057.

Homocysteine and Peripheral Vascular Disease



Boushey, et al. JAMA 1995;274:1049-1057.

Summary

- Plasma homocysteine is a strong, independent, continuous risk factor for atherosclerotic vascular disease.
- Each 5 μmol/L increase in plasma homocysteine, equal to about 1 SD in the normal population is associated with a 60% increase in risk for CHD in men and an 80% increase in women, and a 90% increase risk for cerebrovascular disease in men and women.
- The CHD risk for each 5 μmol/L increase in homocysteine is equivalent to the effect of a 20 mg/dL rise in plasma cholesterol.

Homocysteine in the Elderly

Plasma homocysteine levels rise approximately 25% after 50 years of age and after 60 years of age there is a progressive rise in homocysteine levels with advancing age in men and women that may partially account for the age-related risk for CVD in the elderly.

The rise in plasma homocysteine levels parallels the age-related decrease in serum levels of folate, vitamin B_6 and vitamin B_{12}.

Several biologic mechanisms associated with aging such as malabsorption can result in reduced serum vitamin levels. However, insufficient dietary intake plays a major role.

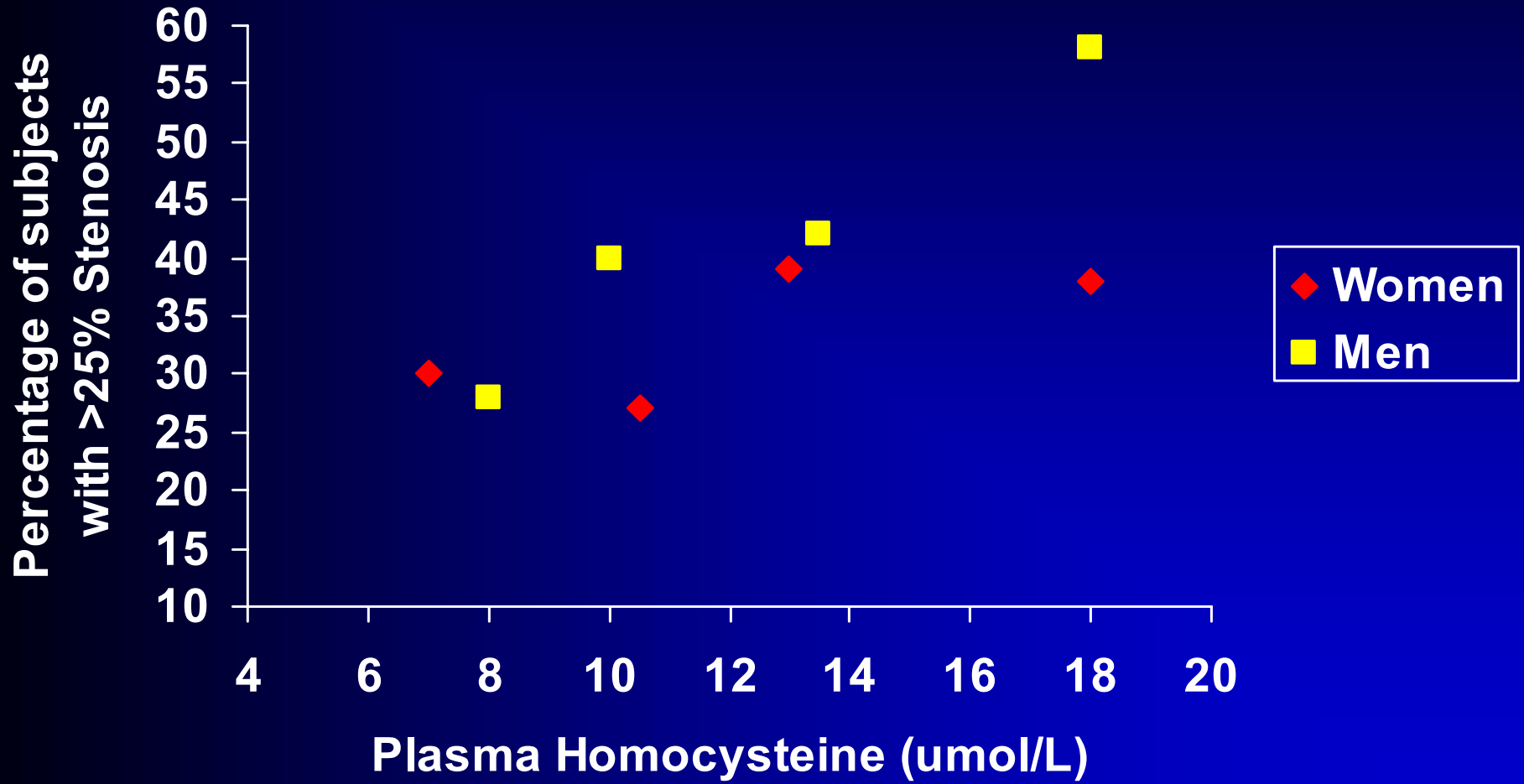
Homocysteine in the Elderly

Data from the Third NHANES indicate the following in individuals >50 years old:

Recommended DV*	% Consumed by women	% Consumed by men
Folate 400 μg	51-58%	62-74%
Vitamin B_6 2 mg	63-70%	84-92%
Vitamin B_{12} 6 μg	43-49%	62-75%

*Daily Value

Association between Plasma Homocysteine Concentrations and Carotid Artery Stenosis



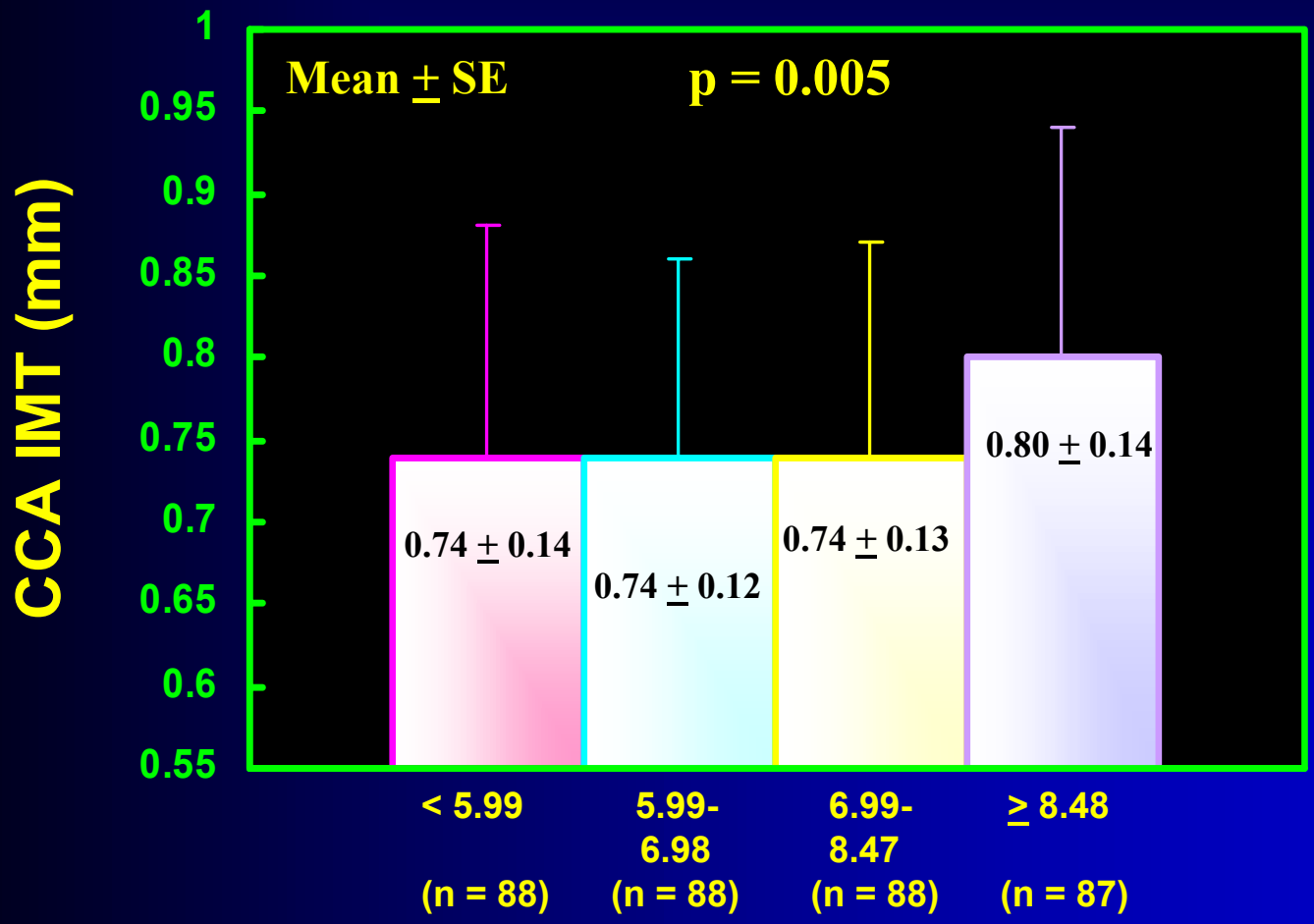
Selhub, et al. NEJM 1995;332:286-291.

Vitamin E Atherosclerosis Prevention Study (VEAPS)

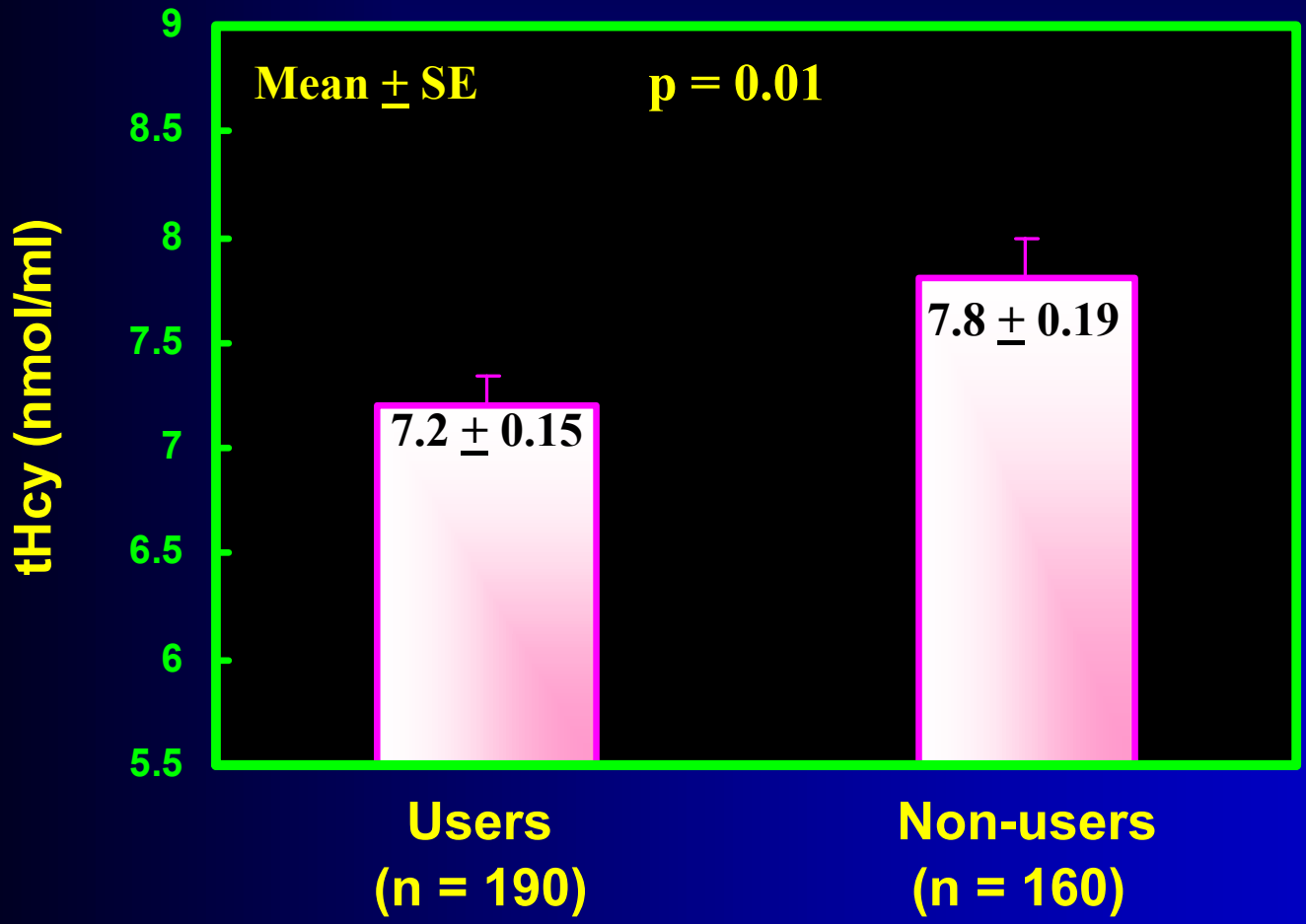
PLASMA HOMOCYSTEINE LEVELS, MULTIVITAMINS USE, AND SUBCLINICAL ATHEROSCLEROSIS

Funded by National Institute on Aging R01-AG13860

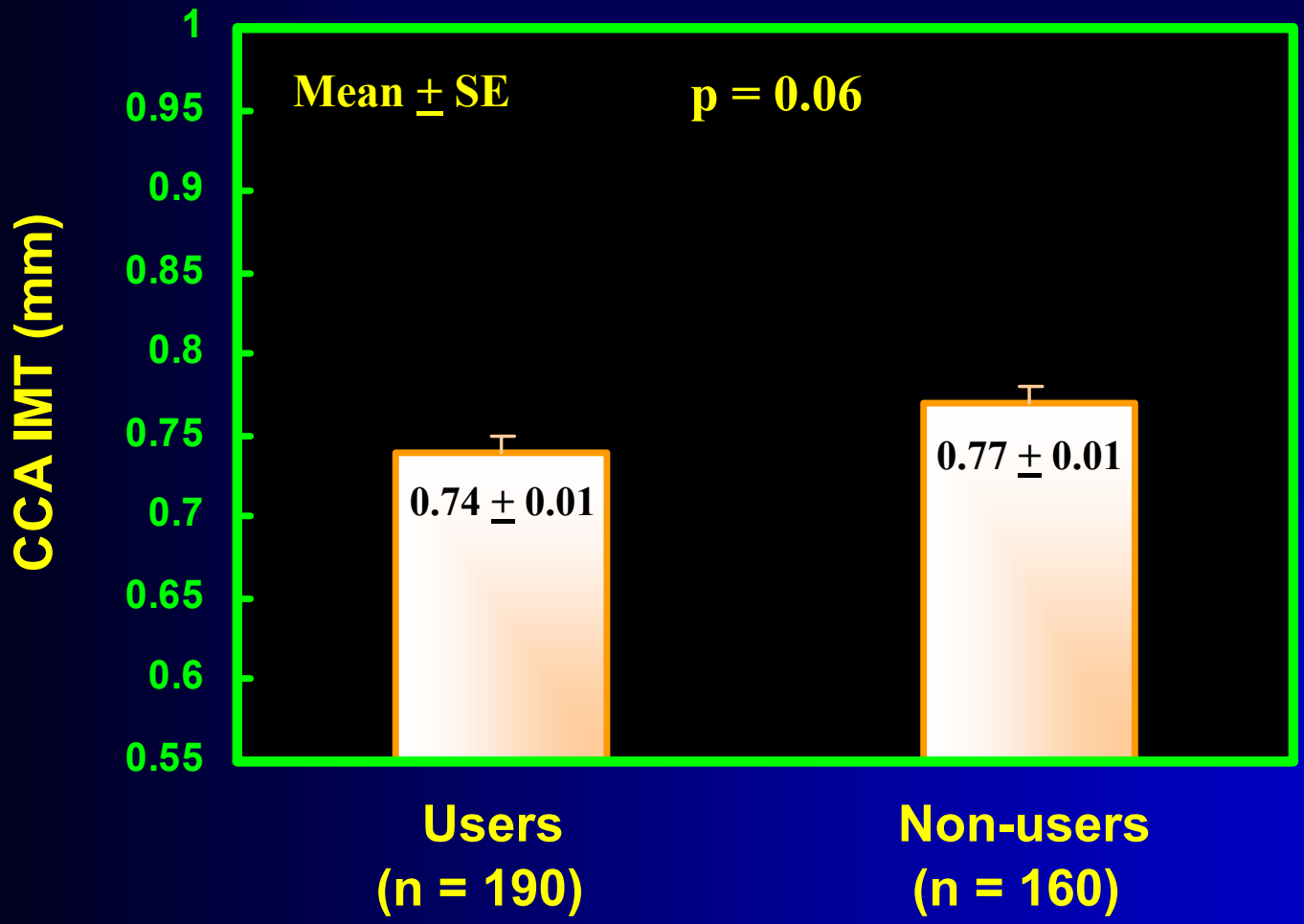
CCA IMT by Quartiles of Fasting Total Plasma Homocysteine Levels in VEAPS



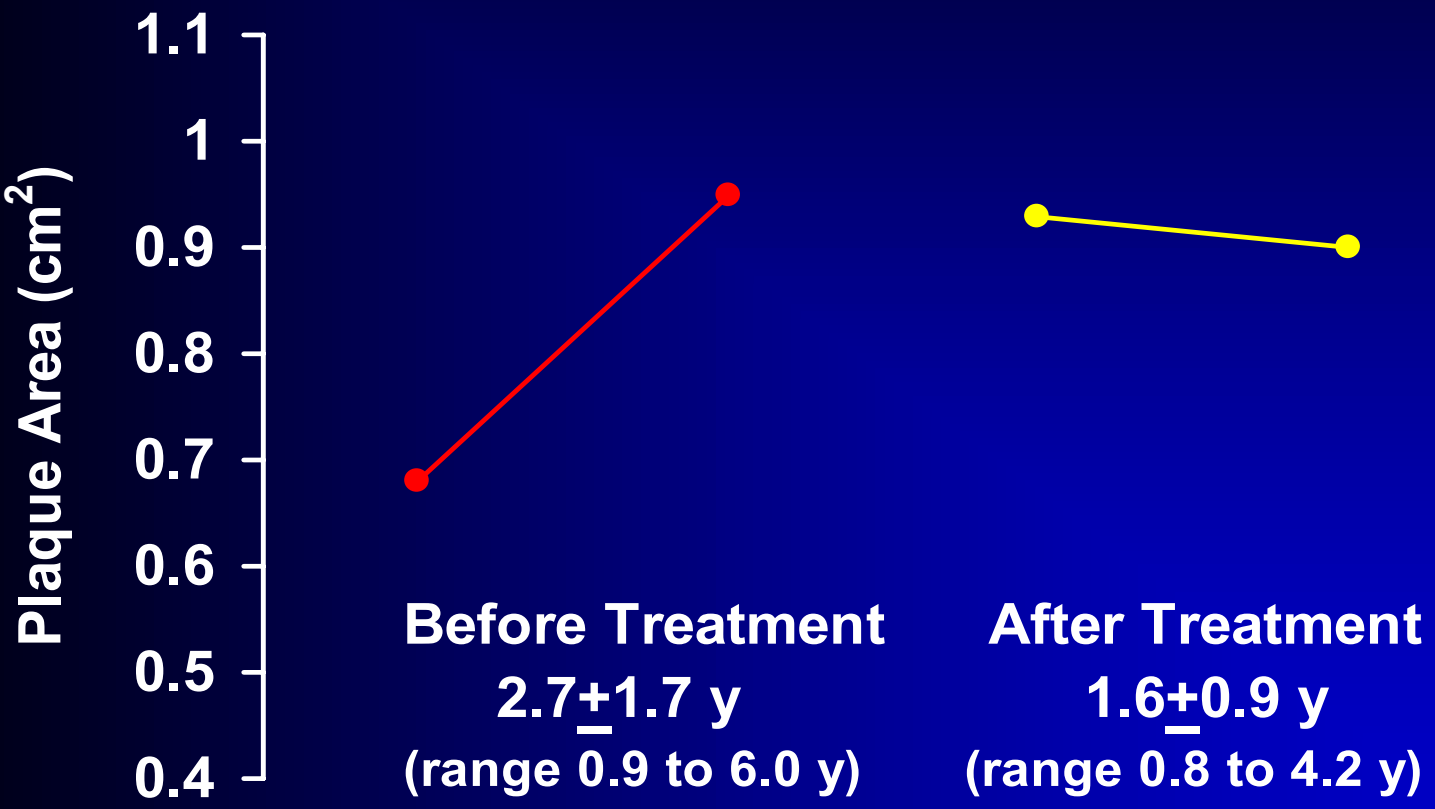
Fasting Total Plasma Homocysteine (tHcy) Levels in Current Multivitamin Users vs Non-Users



CCA IMT in Current Multivitamin Users vs Non-Users



Effect of Homocysteine Lowering on Carotid Plaque (n=100)



Hackam, et al. AJH 2000;13:105-110.

Effect of Homocysteine Lowering on Coronary Artery Restenosis (6 month follow-up)

Variable	Folate+B_6+B_{12} (n=121)	Placebo (n=110)	p-value
Male/Female	80/25	79/21	0.76
Age (yr)	61±11.3	61.1±11.5	0.91
Plasma homocysteine (μmol/L)			
Baseline	11.0±3.9	10.8± 3.9	0.71
Follow-up	7.3±2.4	9.3±3.6	<0.001
Minimum luminal diameter (mm)			
Before PTCA	0.95±0.49	0.86±0.47	0.16
After PTCA	2.33±0.64	2.27±0.57	0.45
At follow-up	1.72±0.76	1.45±0.88	0.02
Degree of stenosis (%)			
Before PTCA	66.8±15.1	69.2±15.6	0.24
After PTCA	23.6±10.1	23.4±10.1	0.85
At follow-up	39.9±20.3	48.2±28.3	0.01

Schnyder, et al. NEJM 2001;345:1593-1600.

Effect of Homocysteine Lowering on Clinical Outcome after PTCA (12 month follow-up)

Event	No.(%) Folate +B_6+B_{12} (n=272)	Placebo (n=281)	Hazard Ratio (95% CI)	p-value
Target lesion revascularization	27(9.9)	45(16)	0.61(0.41-0.95)	0.02
Any revascular	38(14)	56(19.9)	0.69(0.51-0.98)	0.04
Nonfatal MI	7(2.6)	12(4.3)	0.57(0.27-1.42)	0.17
Cardiac death	3(1.1)	6(2.1)	0.51(0.15-2.00)	0.23
Any death	4(1.5)	8(2.8)	0.52(0.21-1.56)	0.17
Any event	42(15.4)	64(22.8)	0.66(0.47-0.94)	0.01

Schnyder, et al. JAMA 2002;288:973-979.

Clinical Trials to Assess the Effect of Homocysteine Lowering on CVD

Trial	Population	n	Intervention
Norwegian Study of Homocysteine Lowering with B-vitamins in Myocardial Infarction (NORVIT)	MI	3000	FA(0.8mg)+B_6(40mg) +B_{12}(0.4mg)
Western Norway B Vitamin and Trial (WENBIT)	CHD	2000	FA(0.8mg)+B_6(40mg) +B_{12}(0.4mg)
Prevention with a Combined Inhibitor and Folate in Coronary Heart Disease (PACIFIC)	CAD or high risk	10000	FA(0.2 or 2mg)
Heart Outcomes Prevention Evaluation-2 (HOPE-2)	MI or high risk	5000	FA(5mg)+B_6(50mg) +B_{12}(1mg)

Clinical Trials to Assess the Effect of Homocysteine Lowering on CVD

Trial	Population	n	Intervention
Vitamin Intervention for Stroke Prevention (VISP)	Stroke	3600	FA(2.5mg)+B_6(25mg) +B_{12}(0.4mg) vs. FA(0.02mg)+B_6(0.2mg) +B_{12}(0.06mg)
Women's Antioxidant and Cardiovascular Disease Study (WACS)	CAD or high risk	5449	FA(2.5mg)+B_6(50mg) +B_{12}(1mg)
Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)	MI	12000	FA(2mg)+B_{12}(1mg)
Cambridge Heart Antioxidant Study (CHAOS 2)	MI or UA	4000	FA(5mg)

B-Vitamin Atherosclerosis Intervention Trial (BVAIT)

Study Design: randomized, double-blind, placebo-controlled trial

Subjects: 490 healthy men and women ≥40 years old without preexisting CVD

Intervention: FA(5mg)+B_6(50mg)+B_{12}(0.4mg) daily placebo

Follow-up: 3 years

1º outcome: rate of change of the right distal far wall CCA IMT in computer image processed B-mode ultrasonograms obtained every 6 months

2º outcome: rate of change of coronary and aortic calcification by multirow CT detection

Conclusions

- More than 40 epidemiological studies consistently indicate that an elevated level of plasma homocysteine is associated with cardiovascular disease.
- Arterial imaging data indicate that the risk for atherosclerosis appears to increase at a plasma homocysteine level of 8.5-9 μmol/L.
- Accumulating data indicate causality between plasma homocysteine levels and cardiovascular disease, but solid evidence will have to await completion of ongoing randomized controlled trials.