Evidence based cardiology

Emerging approaches in preventing cardiovascular disease

Eva M Lonn, Salim Yusuf

Reducing cholesterol and blood pressure, as well as smoking cessation, have been shown to be effective strategies for preventing cardiovascular diseases.[1] However, these "classical" risk factors, along with known non-modifiable risk factors such as age, sex, and family history, cannot fully explain why some people develop myocardial infarction and stroke, while others do not.[2–4] Additional factors may have a role in the pathogenesis of atherosclerosis, and new preventive strategies may be of use. In this article we briefly review the use of antioxidants, the use of angiotensin converting enzyme inhibitors, and homocysteine lowering; other "emerging" cardiovascular risk factors and potential preventive strategies that are under investigation are summarised in table 1.

Summary points

Classical risk factors for atherosclerosis cannot fully explain why certain people develop coronary heart disease and stroke, while others do not

Other potential ("emerging") risk factors for atherosclerosis and new preventive therapies are currently being studied

Promising new preventive therapies include antioxidants, lowering of homocysteine concentrations, decreasing the activation of the renin-angiotensin and the coagulation systems, antibiotics, and anti-inflammatory agents

These therapies have not been proved in clinical trials; at present, the emphasis should be on treating established risk factors and consistently applying therapies that are known to reduce cardiovascular morbidity and mortality

This is the first of four articles

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BMJ 1999;318:1337–41

Oxidative stress and antioxidants

Extensive laboratory data show that oxidative modification of low density lipoprotein cholesterol is an important step in the pathogenesis of atherosclerosis, and experimental studies in different animal models show that antioxidants decrease oxidation of low density lipoprotein cholesterol and reduce plaque formation.[5 6]

Epidemiological studies have generally reported that increased intake of antioxidants through diet or supplements, particularly vitamins E and C and β carotene, is associated with a lower risk of coronary heart disease.[7–9] Other antioxidants, such as other carotenoids, flavonoids, selenium, magnesium, and monounsaturated fat, are also found in natural food products and may reduce oxidation of low density lipoprotein cholesterol. The most compelling results have been with vitamin E supplementation.[10–12] However, these epidemiological studies have several methodological limitations. While most observational studies have attempted to "statistically" adjust for other factors that could affect the cardiovascular risk, such adjustments are difficult and not always adequate. Lifestyle and dietary patterns not accounted for could contribute to some of the observed apparent lower cardiovascular risk in people who use supplemental vitamins in comparison to non-users, and similar confounders could bias the results of epidemiological studies evaluating dietary intake of antioxidant vitamins.Therefore, the role of specific vitamins in the prevention of coronary heart disease is best evaluated in randomised clinical trials.

Trials of vitamin E

Three large randomised placebo controlled trials of vitamin E have been completed (table 2). The alpha-tocopherol beta carotene cancer prevention study (ATBC) was designed primarily to assess the effects of daily supplementation with α tocopherol and β carotene on cancer.[13] A total of 29 133 Finnish male smokers were randomly assigned to α tocopherol (vitamin E) 50 mg daily or placebo and β carotene 20 mg daily or placebo for 5-7 years. Vitamin E did not prevent death from cardiovascular disease or myocardial infarction. The incidence of angina pectoris was modestly reduced (relative risk reduction = 9%, 95% confidence interval 1% to 17%; P = 0.04).[14] In the subgroup of individuals with previous myocardial infarction, modest benefits on non-fatal coronary events but no effect on cardiac mortality were reported.[15] The major limitation of this trial was the vitamin E dose used (50 mg/day), which is much lower than the doses suggested by most of the epidemiological data to be cardioprotective.

A second large primary prevention trial conducted in China reported a marginally significant reduction in total mortality (9%, 0% to 70%) for a combination of vitamin E, β carotene, and selenium, with a trend towards reduced cerebrovascular mortality.[16] The vitamin E dose was also low (30 mg/day), and the population studied was very different from Western populations, having a lower risk of cardiac events and possibly an overall lower consumption of dietary antioxidants. Furthermore, the study design does not allow the identification of the particular antioxidant that contributed to the reduction in mortality.

The Cambridge heart antioxidant study (CHAOS) is a secondary prevention study of 2002 patients with coronary atherosclerosis randomised to vitamin E 800 IU daily or 400 IU daily or placebo. It reported marked reductions in non-fatal myocardial infarction (77%, 53% to 89%; P < 0.001) and in the combined end point of any major cardiovascular event (47%, 17% to 66%; P = 0.005).[17] Although the results are encouraging, this study has many methodological

Table 1 Emerging cardiovascular risk factors and new preventive strategies

Emerging cardiovascular risk factors	New preventive strategies
"Normal" cholesterol, blood pressure, and blood glucose	Lower thresholds of treatment in high risk individuals
Oxidation of low density lipoprotein cholesterol	Antioxidants (such as vitamin E)
Activation of the renin-angiotensin-aldosterone system	Angiotensin converting enzyme inhibitors
Hyperhomocysteinaemia	Folic acid, vitamin B-6, vitamin B-12
Abnormalities of coagulation:	
Fibrinogen	New antithrombotic approaches (such as preventive use of warfarin, new antiplatelet drugs)
Factor VII	
Von Willebrand factor	
Plasminogen activator inhibitor-1	
Lipoprotein Lp(a)	Niacin, oestrogens
Postmenopausal state	Oestrogens, selective oestrogen receptor modulators
Chronic infection and inflammation	Antibiotics, anti-inflammatory agents
Genetic abnormalities	"Targeted" treatment aimed at specific genes or their phenotypic expression
Nutritional factors	
Psychological factors	
Environmental factors	
Socioeconomic factors	

problems and remains inconclusive. The study groups were not balanced at baseline and follow up may not have been complete. The duration of the study was short (median of 510 days), yet the observed magnitude of benefit with vitamin E was large; the experimental and epidemiological data make such a large effect unlikely. Total mortality was slightly higher in the α tocopherol group than in the placebo group (3.5% *v* 2.7%, P = 0.31). Therefore, it would be premature to conclude that vitamin E use reduces coronary risk, and routine use of vitamin E should await the results of the ongoing large trials.[9]

Other antioxidants

β Carotene has been evaluated in three large primary prevention trials in men—all of which failed to show any reduction in the risk of cardiovascular events and cancer (table 2).[13 18 19] Furthermore, in two studies there were concerns about increased risk of cancer. These data suggest that raised β carotene concentrations may have been a marker associated with other cardioprotective factors.

There have been no large trials of vitamin C supplementation. In a trial of 578 patients admitted to a geriatric hospital, supplementation with 200 mg of vitamin C daily did not reduce mortality at six months.[20] In the Chinese trial discussed above there was no reduction in total mortality and in mortality from cerebrovascular disease in people randomised to a combination of vitamin C and molybdenum.[16]

Probucol is a lipid lowering agent which also reduces high density lipoprotein cholesterol and has potent antioxidant properties. In the probucol quantitative regression Swedish trial (PQRST), probucol failed to retard progression of femoral atherosclerosis.[21] More recently a reduction in restenosis rates after coronary angioplasty was reported in a randomised trial of probucol,[22] providing renewed interest in this agent, although this study has several limitations and conclusions should await confirmation in additional trials.

Summary

Though it is attractive, the antioxidant hypothesis has not been proved in clinical trials. The most promising data relate to vitamin E, but these are inconclusive and do not warrant its widespread use at present. The

Table 2 Large randomised trials of antioxidant vitamins

Trial	Study participants	Follow up (years)	Vitamin dose	Outcomes	% Reduction in relative risk (95% CI)
Trials of vitamin E					
Alpha-tocopherol, beta carotene cancer prevention study (ATBC)[13 14 15]	29 133 male smokers in Finland	6.1	50 mg/day	Total mortality	–2 (–9 to 5)†
				Death from cardiovascular disease	2 (–8 to 11)
				Angina	9 (1 to 17)
Chinese study[16]	29 584 adults in Linxian province	5.2	30 mg/day*	Total mortality	9 (0 to 17)
				Death from cerebrovascular disease	9 (–8 to 24)
Cambridge heart antioxidant study (CHAOS)[17]	2002 patients with coronary artery disease in the United Kingdom	1.4	800 IU or 400 IU/day	Total mortality	–29 (–119 to 24)
				Death from cardiovascular disease	–10 (–96 to 39)
				Non-fatal myocardial infarction	77 (53 to 89)
Trials of β carotene					
Alpha-tocopherol, beta carotene cancer prevention study (ATBC)[13 14]	29 133 male smokers in Finland	6.1	20 mg/day	Total mortality	–9 (–17 to –2)†
				Death from cardiovascular disease	–11 (–23 to 1)
				Death from cancer	–9 (–23 to 3)
β Carotene and retinol efficacy trial (CARET)[18]	18 314 male smokers, former smokers and workers exposed to asbestos in the United States	4.0	30 mg/day‡	Total mortality	–17 (–33 to –3)
				Death from cardiovascular disease	–26 (–61 to 1)
				Death from cancer	–46 (–100 to –7)
Physicians health study (PHS)[19]	22 071 male physicians in the United States	12.0	50 mg/alternate days	Total mortality	–2 (–11 to 7)
				Death from cardiovascular disease	–9 (–27 to 7)
				Death from cancer	–2 (–18 to 11)
Skin cancer prevention study (SCPS)[19a]	1188 men and 532 women in the United States	8.2	50 mg/day	Total mortality	–3 (–30 to 18)
				Death from cardiovascular disease	–16 (–64 to 18)
				Death from cancer	17 (–29 to 56)

*In addition to vitamin E, selenium and β carotene supplements were used.
†Minus sign indicates an increased risk.
‡Patients randomised to β carotene also received 25 000 U/day of retinol (vitamin A)

Table 3 Effects of angiotensin converting enzyme (ACE) inhibitors on myocardial infarction in patients with low ejection fraction

Trial	Patient characteristics	No (%) with myocardial infarction		% Reduction in relative risk (95% CI)	P value
		ACE inhibitor	Placebo		
Acute infarction ramipril efficacy (AIRE)[30]	Clinical evidence of heart failure soon after infarct	81 (8.0)	88 (8.9)	9 (–22 to 35)*	>0.05
Trandolapril cardiac evaluation study (TRACE)[31]	Left ventricular ejection fraction ⩽35% soon after infarct	97 (11.1)	111 (12.7)	14 (–10 to 31)	>0.05
Studies of left ventricular dysfunction (SOLVD)[32]:					
Prevention	Left ventricular ejection fraction ⩽35% without heart failure	161 (7.6)	204 (9.1)	24 (6 to 38)	0.01
Treatment	Left ventricular ejection fraction ⩽35% with heart failure	127 (9.9)	158 (12.3)	23 (2 to 39)	0.02
Survival and ventricular enlargement trial (SAVE)[33]	Left ventricular ejection fraction ⩽40% soon after infarct	133 (11.9)	170 (15.2)	25 (5 to 40)	0.05
Total				23 (11 to 32)	

*Long term follow up of the UK component of AIRE (AIREX) showed a significant reduction in fatal myocardial infarctions.

strong biological rationale and epidemiological data relating antioxidants to lower cardiovascular risk justify ongoing trials of vitamin E and experimentation with new antioxidant agents in further evaluating this hypothesis.

Impact of angiotensin converting enzyme inhibitors

Experimental and clinical studies show that angiotensin converting enzyme inhibitors may reduce cardiovascular risk through cardioprotective and vasculoprotective effects mediated by blocking both circulating and tissue renin-angiotensin systems, as well as by bradykinin potentiation.[23] Angiotensin converting enzyme inhibitors are antiproliferative, have antimigratory effects on smooth muscle cells, improve endothelial function, may act as antioxidants, and act as antithrombotic agents by decreasing platelet aggregation and enhancing endogenous fibrinolysis.[23–25] Several epidemiological and genetic studies have shown a link between the renin-angiotensin system and the risk for myocardial infarction,[26 27] although these findings were not confirmed in other reports and remain controversial.[28 29]

Risk reduction

Randomised clinical trials in symptomatic and asymptomatic patients with documented coronary heart disease and left ventricular dysfunction who were treated with angiotensin converting enzyme inhibitors for approximately 40 months showed a significant reduction in the risk of myocardial infarction. Pooled analyses of the five major trials of angiotensin converting enzyme inhibitors in patients with low left ventricular ejection fraction indicate a 23% reduction in the risk for myocardial infarction associated with treatment with angiotensin converting enzyme inhibitors (table 3). In addition, reductions in other ischaemic end points were also significant in treated patients: hospital admissions for unstable angina in the studies of left ventricular dysfunction (SOLVD) trials, 20%, 9% to 29%; P = 0.001; revascularisation procedures in the survival and ventricular enlargement trial (SAVE), 24%, 6% to 39%; P = 0.01. Because these trials were conducted in patients with low left ventricular ejection fraction or symptomatic heart failure, who were likely to have raised concentrations of renin and angiotensin, these data cannot be extrapolated to other patient populations. However, the reduction in ischaemic events was seen in several different subgroups and was not explained by the haemodynamic action of the angiotensin converting enzyme inhibitors alone. The role of these drugs in preventing myocardial infarction in high risk patients with preserved left ventricular function is under investigation in several large clinical trials.[34]

SUE SHARPLES

Summary

Angiotensin converting enzyme inhibitors are currently indicated in all patients with clinical manifestations of heart failure and in individuals with asymptomatic left ventricular dysfunction. These agents have also a proved role in the treatment of acute myocardial infarction, hypertension and diabetic nephropathy. The preventive use of angiotensin converting enzyme inhibitors in high risk individuals with preserved left ventricular function, while promising, should await results of ongoing large clinical trials.

Homocysteine and vascular disease

Homocysteine, an amino acid containing sulphur, is produced during catabolism of the essential amino acid methionine. It can be irreversibly degraded by cystathionine β-synthase; the process requires vitamin B-6 as a cofactor. It can be remethylated to conserve methionine in a process requiring methionine

synthase and methylcobalamin (vitamin B-12) as a cofactor and methyltetrahydrofolate reductase (MTHFR) as a cosubstrate. This metabolic pathway requires an adequate supply of folate and the enzyme MTHFR. Genetic and acquired abnormalities in the function of these enzymes, or deficiencies in folate or vitamin B-6 or B-12 cofactors, can therefore lead to raised homocysteine concentrations. Extremely high concentrations are accompanied by homocystinuria and are caused by rare genetic enzyme deficiencies. People with these distinct genetic abnormalities typically develop severe premature atherosclerotic and thromboembolic disease, and this led McCully to formulate the homocysteine theory of atherosclerosis.[35] More recently, a role for modest increases in homocysteine, caused by a variety of genetic, physiological, pathological, and nutritional factors, has been proposed in the aetiology of atherosclerotic and thromboembolic vascular disease.

Vascular injury has been experimentally induced by homocysteine. Typical features include endothelial dysfunction, due to direct toxic endothelial cell damage and impaired production of nitric oxide, smooth muscle cell proliferation, increased production of reactive oxygen radicals, increased susceptibility of low density lipoprotein cholesterol to oxidation, and increased thrombogenicity.[36]

Graded relation to risk

A large number of investigations, mostly cross sectional or retrospective case-control epidemiological studies, found associations between raised homocysteine concentrations and increased cardiovascular risk. A meta-analysis of the major epidemiological studies up to 1995 reported a linear, independent relation between homocysteine concentrations and cardiovascular risk.[37] Every 5 µmol/l increment in homocysteine was found to be associated with increased risk for coronary artery disease (odds ratio = 1.7, 1.5 to 1.9), for cerebrovascular disease (1.5, 1.3 to 1.9) and for peripheral vascular disease (fewer studies available and less robust quantitation of risk). Importantly, a graded risk of adverse cardiovascular events throughout the "normal" range of homocysteine concentrations was shown, suggesting that even people with "normal" homocysteine concentrations might benefit from treatments that lowered homocysteine (a similar relation to cardiovascular risk as cholesterol). More recently the European Concerted Action Project reported an increased relative risk per 5 µmol/l increment in fasting total homocysteine concentration of 1.35 (1.1 to 1.6) for men and 1.42 (0.99 to 2.05) for women,[38] and Nygard et al found a strong graded relation between homocysteine concentration and mortality in patients with angiographically confirmed coronary artery disease.[39] Low dietary intake as well as low circulating concentrations of folate and vitamins B-6 and B-12 have also been associated with increased cardiovascular risk, presumably due to resultant hyperhomocysteinaemia.[40 41] Prospective cohort studies have not always found a consistently clear relation between raised homocysteine concentrations and cardiovascular risk.[42]

Homocysteine can be easily and effectively reduced by supplementation with folic acid alone or in combination with vitamins B-6 and B-12. These represent very simple, inexpensive, and generally risk free interventions, but clinical trials of homocysteine lowering have not been conducted thus far. Several randomised clinical trials evaluating the impact of folate supplementation alone or combined with vitamin B-6 and B-12 in reducing major clinical cardiovascular events and on progression of atherosclerosis are currently underway.

Summary

The current experimental and epidemiological data suggest that reducing homocysteine concentrations represents an effective, cheap, and simple intervention. Until confirmation from clinical trials is available, it seems prudent to ensure adequate dietary intake of folate and vitamins B-6 and B-12.

Conclusions

This review summarises the evidence on antioxidants, modulating the renin-angiotensin axis, and reducing homocysteine concentrations as potential new preventive cardiovascular interventions. These areas are promising, but definite conclusions must await the results of randomised clinical trials. Other promising preventive strategies include aggressive lowering of blood glucose in diabetic patients and in people with only modest increases in plasma glucose; postmenopausal use of hormone replacement and of selective oestrogen receptor modulators; use of antibiotics; modifcation of determinants of coagulation; enhancing fibrinolysis; lowering lipoprotein Lp(a); and modifying psychosocial factors.

This article is adapted from *Evidence-Based Cardiology*, edited by S Yusuf, J A Cairns, A J Camm, E L Fallen, and B J Gersh, which was published by BMJ Books in 1998.

Competing interests: EML has received reimbursement for presentations (honorarium as speaker) from several companies, including Hoechst Marion Roussel, Parke-Davis, Merck Sharpe Dohme, Fournier, and has attended several symposiums which included a reimbursement fee. She is coprincipal, principal, or coinvestigator on several grants with industry support (Hoechst Marion Roussel, Parke-Davis).

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Corrections and clarifications

Minerva pictures
The report of a subclavian artery aneurysm by S Sudhindran (30 January, p 340) should also have been credited to G T Abbott, consultant radiologist, and P R Edwards, consultant vascular surgeon, and the aneurysm was stented by the radiologist Dr Abbott rather than by "surgeons." The report of a haemophilic patient's verruca by C H Ashton (13 February, p 474) wrongly stated that liquid nitrogen was injected; liquid nitrogen is applied topically by spray or cotton bud.

Coeliac disease in primary care: case finding study
In this general practice paper by Harold Hin and colleagues (16 January, pp 164-7) the results section of the abstract should have stated that the specificity of the endomysial antibody test was 100% (rather than 30/30), and in the second paragraph of the subsection on laboratory testing (p 164) low titres of IgA were considered to be those <0.3 g/l (not 0.3 mg/l).

Haemolytic uraemic syndrome and E coli O157
A typesetting error in this editorial by Margaret Fitzpatrick (13 March, pp 684-5) resulted in the serotype of *Escherichia coli* being wrongly labelled 0157 rather than O157.

Scientists discover a gene involved in diabetes and obesity
This news article by Deborah Josefson (13 March, p 689) used the wrong abbreviation for the enzyme protein tyrosine phosphate 1B. The abbreviation should have been PTP-1B not PTB-1B.

ABC of labour care: Place of birth
This article by Luke Zander and Geoffrey Chamberlain (13 March, pp 721-3) contains an error in the table of recent data from two midwifery delivery units (p 722): the heading of the second column should have been "No of bookings (labours)" not "No of bookings (births)."

Fortnightly review: Acute urinary retention in men: an age old problem
The authors' addresses were misplaced in this article by Mark Emberton and Ken Anson (3 April, pp 921-5). Thus, Mr Emberton works at the Institute of Urology and Nephrology, University College London, and Dr Anson works at St George's Hospital NHS Trust, London.