PRIMARY PREVENTION OF ATHEROSCLEROTIC VASCULAR DISEASE

Preventing atherosclerosis before it leads to death and disability should now be possible using lifestyle modification and drugs where necessary.

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Atherosclerosis is one of the most common causes of death and disability throughout the world. Cardiovascular diseases are expected to be the main cause of death glob ally within the next 15 years owing to a rapidly increasing prevalence in developing countries and Eastern Europe and the rising incidence of obesity and diabetes in the Western world. Coronary artery atherosclerosis has been a major focus for clinical investigation and considerable strides have been made in the development of programmes to prevent and treat the clinical manifestations of this disease. However atherosclerosis is a systemic disease with important sequelae in many other regional circulations – including those supplying the brain, kidneys, mesentery and limbs.

Predisposition to atherosclerosis begins in childhood. Atherosclerosis is a process that starts early in life and progresses silently and slowly for decades, usually only manifesting clinically in middle age. Since childhood risk factors persist into adulthood, the lifelong burden of a dyslipidaemic trait and concomitant conditions such as obesity and hypertension has a major impact on the silent phase of this disease. The main objectives of primary prevention are to reduce morbidity, to improve quality of life and to increase life expectancy. There is growing evidence that lifestyle changes and primary risk factor modification can reduce both morbidity and mortality.

TRADITIONAL RISK FACTORS

The major risk factors for atherosclerosis are age, family history, dyslipidaemia, cigarette smoking, hypertension and diabetes. These risk factors rarely occur in isolation. The Framingham study demonstrates the importance of multiple risk factors for coronary artery disease (CAD) events. Asymptomatic individuals are classified into low risk (0 - 1 risk factor), intermediate risk (≥ 2 risk factors but < 10% risk of CAD over 10 years), moderately high risk (≥ 2 risk factors and 10 - 20% risk of CAD over 10 years), or high risk (≥ 2 risk factors and > 20% risk of CAD over 10 years). Risk is calculated by adding the points from each risk category and the absolute 10-year risk is derived from the total score. The Framingham risk scoring (Table I, p.203) can be used to determine the 10-year risk for developing CAD. To calculate risk, add the points of each category. The absolute 10-year risk is derived from the total score.

Table II. **LDL cholesterol and cut-off points for therapeutic lifestyle changes and drug therapy – the NCEP III guidelines and proposed modifications (in italics) based on recent clinical trial evidence.**

Risk category	LDL goal (mmol/l)	Therapeutic lifestyle changes to be initiated (mmol/l)	Drug therapy to be initiated (mmol/l)
High risk: CAD or CAD risk equivalents (10-year risk > 20%)	< 2.59 *Optional goal is 1.80*	≥ 2.59	≥ 3.36 (2.59 - 3.35: drug optional) *≥ 2.59 (<2.59 consider drug options)**
Moderately high risk: ≥ 2 risk factors (10-year risk 10 - 20%)	< 3.36	≥ 3.36	≥ 3.36 *2.59 - 3.35: consider drug options†*
Lower risk: 0 - 1 risk factor (< 10% 10-year risk)	< 4.14	≥ 4.14	≥ 4.92 (4.14 - 4.91: drug optional)

* If baseline LDL cholesterol is < 2.59mmol/l, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results.
† For moderately high-risk persons, when LDL cholesterol level is 2.59 - 3.35mmol/l, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL cholesterol level < 2.59 mmol/l is a therapeutic option based on available clinical trial results.

The current National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) report includes diabetes mellitus (as well as peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease) as a CAD risk equivalent. A low level of HDL cholesterol is an independent risk factor for future cardiovascular events. Low HDL is defined as less than 1.03 mmol/l in men and less than 1.30 mmol/l in women. Epidemiological studies have indicated that each increase in baseline HDL cholesterol of 0.03 mmol/l is associated with a 6% decrease in the risk of death from coronary disease or myocardial infarction. See Table II for cut off points for lifestyle changes and drug treatment.

The effect of multiple risk factors seems to accelerate the extent of atherosclerosis in both the aorta and coronary arteries and cardiovascular risk factors become additive in their effect on cardiovascular disease events in adults. There is a need for a treatment paradigm shift from the diagnosis and treatment of individual risk factors to the assessment and management of total cardiovascular disease risk.

Clustering of CAD risk factors such as hypertension and dyslipidaemia may begin in childhood, indicating a need for screening for cardiovascular risk early in life. There is also a need for educational measures to improve the level of awareness among the general population about adopting healthy lifestyle options early on in life. Individuals with co-existing hypertension and dyslipidaemia are particularly likely to develop atherosclerosis and the physiological interplay of these two diseases results in a marked increase in CAD risk. A recent study showed that the prevalence of CAD was more than doubled in patients with concomitant hypertension and dyslipidaemia. Clinically meaningful reductions in blood pressure and serum cholesterol concentrations can be achieved by lifestyle modifications which include weight loss, dietary intervention and regular aerobic exercise.

Evidence from research indicates that atherosclerosis is, at least partially, genetically determined. Carotid artery intimal-medial thickness, a surrogate marker of atherosclerosis, is highly heritable. Independent from the major risk factors, no major gene has yet been identified for atherosclerosis. Research efforts are now focused on discovering genes that contribute to the intermediate traits that are more proximal on the pathway leading to atherosclerosis.

METABOLIC SYNDROME

Obesity increases the prevalence and persistence of multiple risk factor clustering. Childhood obesity has been shown to be the driving force related to the metabolic syndrome. The term metabolic syndrome refers to a specific collection of disorders and the diagnosis of this syndrome is based on the presence of 3 or more stipulated risk factors. These include abdominal obesity, atherogenic dyslipidaemia (elevated triglycerides, small LDL particles, low HDL cholesterol), raised blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states. These risk factors enhance the risk for CAD at any given level of LDL cholesterol. CAD has been shown to be more prevalent in those individuals with the metabolic syndrome than those without (13.9% versus 8.7%).

The current NCEP ATP III report acknowledges the importance of this syndrome as a secondary therapeutic target. The recently proposed amendments to these guidelines suggest that the metabolic syndrome should be considered as a factor favouring LDL-lowering drug therapy as a therapeutic option for patients at moderately high risk.

THERAPY

Aggressive statin therapy

Clinical trial evidence supports the benefits of cholesterol reduction in the presence of atherosclerosis or multiple risk factors – even if LDL cholesterol is not elevated. The results of these trials indicate that lipid-lowering

Table I. **The Framingham Risk Scoring System**

• Total cholesterol (TC)

TC (mmol/l)	Age 20 - 39		Age 40 - 49		Age 50 - 59		Age 60 - 69		Age 70 - 79	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
< 4.1	0	0	0	0	0	0	0	0	0	0
4.2 - 5.2	4	4	3	3	2	2	1	1	0	1
5.3 - 6.2	7	8	5	6	3	4	1	2	0	1
6.3 - 7.2	9	11	6	8	4	5	2	3	1	2
≥ 7.2	11	13	8	10	5	7	3	4	1	2

• Smoking status

	Age 20 - 39		Age 40 - 49		Age 50 - 59		Age 60 - 69		Age 70 - 79	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Non-smoker	0	0	0	0	0	0	0	0	0	0
Smoker	8	9	5	7	3	4	1	2	1	1

• Systolic BP

Systolic BP (mmHg)	Untreated		Treated	
	Male	Female	Male	Female
< 120	0	0	0	0
120 - 129	0	1	1	3
130 - 139	1	2	2	4
140 - 159	1	3	2	5
≥ 160	2	4	3	6

• Age

Age	Male	Female
20 - 34	–9	–7
35 - 39	–4	–3
40 - 44	0	0
45 - 49	3	3
50 - 54	6	6
55 - 59	8	8
60 - 64	10	10
65 - 69	11	12
70 - 74	12	14
75 - 79	13	16

• HDL

HDL (mmol/l)	Male	Female
≥ 1.56	–1	–1
1.30 - 1.55	0	0
1.04 - 1.29	1	1
< 1.04	2	2

• Total points

Total points Male	10-year risk Male	Total points Female	10-year risk Female
< 0	< 1	< 9	< 1
0	1	9	1
1	1	10	1
2	1	11	1
3	1	12	1
4	1	13	2
5	2	14	2
6	2	15	3
7	3	16	4
8	4	17	5
9	5	18	6
10	6	19	8
11	8	20	11
12	10	21	14
13	12	22	17
14	16	23	22
15	20	24	27
16	25	≥ 25	≥ 30
≥ 17	≥ 30	N/A	N/A

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therapy should be administered to all patients with hypertension regardless of their lipid levels. Previously it was considered optimal to lower the LDL cholesterol level to less than 2.59 mmol/l (Table I). That axiom has now been called into question because clinical trials have shown that atherosclerotic progression and clinical outcomes will be lessened by much more aggressive use of statins. To date, 6 large primary prevention trials with cholesterol-lowering agents have been published. The most important of these in terms of their clinical application are the West of Scotland Coronary Prevention Study Group (WOSCOPS), the AFCAPS and ASCOT-LLA trials. The major finding of all these trials is an early and dramatic reduction in clinical events in treated patients who have a baseline LDL cholesterol > 4.0 mmol/l or an LDL cholesterol level that was previously considered normal that did not warrant drug therapy. More aggressive care of patients with multiple risk factors is the major focus of updated treatment guidelines. In addition, it is now accepted that patients who have no overt CAD but who have multiple risk factors are at risk and should receive treatment for these risk factors to reduce later development of CAD.

A study that evaluated aggressive treatment of elevated blood sugar, blood pressure, LDL cholesterol and triglycerides showed a 53% decrease in CAD events compared with a conventional approach and supports the concept of intensive concomitant risk factor modification in patients at high risk for CAD. Recent calculations indicate that patients at moderate risk should have risk factor modification implemented 15 - 20 years earlier than suggested by conventional algorithms. Recent data also indicate that the Framingham risk function significantly underestimates the 10-year absolute risk of CAD. In Europe, the recommendations of the Third Joint Task Force of European and Other Societies on the Prevention of CAD in Clinical Practice have adopted the European Society of Cardiology SCORE risk prediction system. This allows physicians to estimate the 10-year risk of fatal CAD in asymptomatic subjects with the aim of adjusting the intensity of preventive therapy.

Only a fraction of the patients who should be treated with a statin are currently receiving such therapy. It is estimated that worldwide more than 200 million people meet the criteria for treatment but fewer than 25 million receive statins. One of the main reasons for this degree of undertreatment is cost related. This is especially pertinent in a country such as South Africa, where health care resources are limited.

Lifestyle interventions

Lifestyle interventions are crucially important in the control of obesity, dyslipidaemia and diabetes. Such interventions have also been shown to raise HDL levels. Recently, large prospective studies have shown that healthy diet, exercise and low serum cholesterol as well as normal blood pressure together with smoking abstinence is associated with low risk for CAD. Recommendations for diet, weight loss and exercise offer little or no risk to the patient but have been shown to yield significant long-term benefits. In addition, health education programmes aimed at school children are vital and sorely lacking in this country. Health education is an important tool in setting the stage to encourage children to take care of their own health and be responsible for their well-being. This is a major component of preventive cardiology.

NOVEL RISK FACTORS

CAD events have been predicted using various equations that include the traditional risk factors as variables. Novel risk factors are emerging, however, which may prove to be the key to improving the current risk estimation approach which is lacking in certain respects. Cholesterol screening, for instance, fails to identify almost 50% of the 1.3 million individuals who develop myocardial infarctions in America every year. In addition, much of the total incidence of CAD occurs in individuals with below-average plasma levels of cholesterol.

The compelling evidence for the role of inflammation in atherosclerotic disease has motivated research into the role of other new, risk factors. Atherosclerosis is not solely a disease of lipid deposits, and systemic inflammation plays a crucial role in atherosclerotic inception and progression. Triggers of this inflammatory response may include oxidised lipoproteins, hypertension, diabetes and obesity. Measurement of inflammatory markers may enhance the current risk evaluation.

C-reactive protein

One of the most researched novel markers is C-reactive protein (CRP). Plasma CRP has a long half-life, exhibits stable levels in individuals and has negligible circadian variation. It is easily measured and inexpensive standardised high-sensitivity assays provide similar results in fresh, stored or frozen plasma. Data from prospective studies demonstrate that plasma CRP levels predict the likelihood of CAD events in apparently well people. These data also indicate that high-sensitivity CRP (hs-CRP) measurements add to the predictive ability of plasma lipid risk factors. Elevated plasma CRP levels have been

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The knowledge that atherosclerosis is an inflammatory disease offers exciting new opportunities for the future prediction, prevention and treatment of CAD.

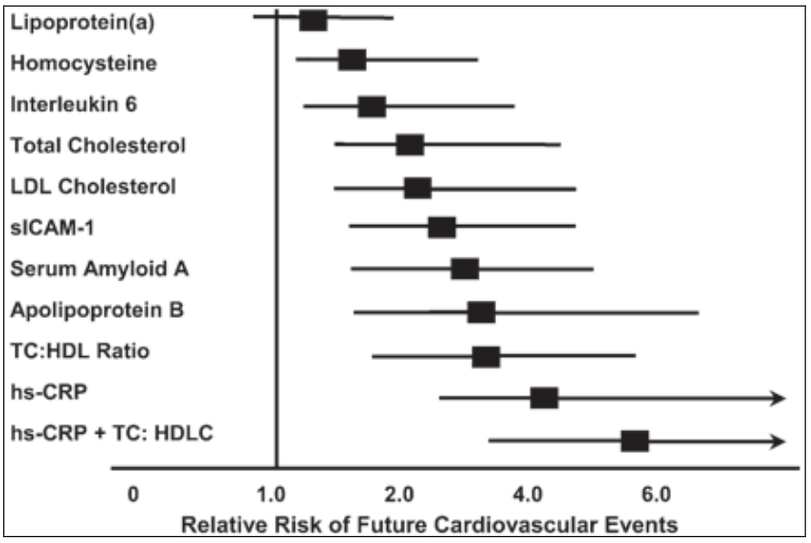

Fig. 1. Direct comparison of CRP to several other lipid and nonlipid risk factors for CAD (HDL-C = HDL cholesterol; LDL-C = LDL cholesterol; TC = total cholesterol).

associated with increased relative risk of initial myocardial infarction at every level of the plasma total cholesterol to HDL cholesterol ratio in apparently healthy men. Plasma hs-CRP level at baseline predicted risk for first CAD events better than baseline plasma LDL cholesterol. Plasma hs-CRP measurement also aided risk prediction in individuals with the metabolic syndrome. An accumulation of components of the metabolic syndrome (central obesity, elevated triglycerides, low levels of HDL, hypertension, elevated blood glucose) were also associated with increased plasma hs-CRP levels.

In 2003 the American Heart Association and the Centers for Disease Control and Prevention published a joint scientific statement recommending the measurement of plasma hs-CRP for assessing absolute risk for coronary disease primary prevention. The current recommended plasma hs-CRP cut-off points are < 1.0 mg/l for low risk, 1.0 - 3.0 mg/l for average risk and > 3.0 mg/l for high risk. In order to assess risk of future first coronary events, each patient is classified into a quintile of risk, depending on the hs-CRP concentration. The reporting of hs-CRP results focuses on the quintile of risk and not the actual mass concentration. Models containing both hs-CRP and total cholesterol or the total cholesterol to HDL ratio are better able to predict future first coronary events than those containing hs-CRP alone (Fig. 1).

The computed relative risk does not vary significantly between men and women and so there is a single risk assessment algorithm for both genders (Table III).

Although there are no specific therapies to decrease hs-CRP and there is no direct evidence that risk of future cardiovascular events is reduced by decreasing hs-CRP, studies have shown that aspirin and pravastatin are effective in decreasing the incidence of future coronary events in those with increased hs-CRP (> 2.1 mg/l). Clinical trials are currently ongoing to further explore the interaction between pravastatin, aspirin and the inflammatory response in primary and secondary settings.

Future investigations will determine whether plasma hs-CRP can identify individuals who are apparently at low risk but may still benefit from lipid-lowering therapy. A large-scale randomised clinical trial (JUPITER) will evaluate the effects of statin therapy in subjects who have both plasma LDL cholesterol levels below those currently used to target therapy and plasma hs-CRP levels that indicate heightened risk of a CAD event. The rationale and design of this trial have been

Table III. **Relative risk estimates for future coronary events in men and women associated with quintiles of hs-CRP and TC:HDL cholesterol ratio.**

Quintile of TC: HDL-C ratio	Men	Women	hs-CRP quintile (< 0.7mg/l)	hs-CRP quintile 2 (0.7 - 1.1 mg/l)	hs-CRP quintile 3 (1.2 - 1.9 mg/l)	hs-CRP quintile 4 (2.0 - 3.8 mg/l)	hs-CRP quintile 5 (3.9 - 15.0 mg/l)
1	< 3.4	< 3.4	1	1.2	1.4	1.7	2.2
2	3.4 - 4.0	3.4 - 4.1	1.4	1.7	2.1	2.5	3
3	4.1 - 4.7	4.2 - 4.7	2	2.5	2.9	3.5	4.2
4	4.8 - 5.5	4.8 - 5.8	2.9	3.5	4.2	5.1	6
5	> 5.5	> 5.8	4.2	5	6	7.2	8.7

published. These results should provide important information regarding the use of plasma hs-CRP values to guide initiation of lipid-lowering therapy in a primary prevention population deemed to be at low cardiovascular risk by means of current criteria. This trial will supply the first findings regarding the clinical application of the biology of inflammation in atherosclerosis.

CONCLUSION

The field of atherosclerotic vascular disease has been advancing at an increasing pace as the importance of the disease and its early recognition is better appreciated by the medical community. The family doctor's office is the ideal location to implement behavioural change strategies which are an integral part of primary prevention. Health care providers should be reminded that a holistic approach is necessary for any primary prevention programme to be successful and no risk factor should be viewed in isolation. The knowledge that atherosclerosis is an inflammatory disease offers exciting new opportunities for the future prediction, prevention and treatment of CAD. This knowledge will hopefully lead to the discovery of new treatments for this life-threatening disease which is the second most common cause of death in South Africa. A commitment to continued education is vital to ensure that South African practitioners remain informed of current trends and new therapeutic options in order that we continue to offer patients the best in clinical care.

Further reading

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IN A NUTSHELL

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