

ATHEROSCLEROSIS AND ARTERIAL STIFFNESS

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INTRODUCTION

Cardiovascular disease is the leading cause of death in developed countries (1). Atherosclerotic coronary artery disease is the commonest form of cardiovascular disease accounting for around 1/3rd of all cause mortality in people over the age of 35. As many of the developing nations adopt more affluent life styles, we are seeing increasing rates of cardiovascular disease in those areas (2). There are numerous studies now confirming that atherosclerosis commences very early in life.

Atherosclerosis is defined as the deposition of fatty substances, inflammatory cells and mediators in the subendothelial layer of blood vessels, eventually leading to thickening and hardening of medium to large sized arteries. Atherosclerosis has a very long pre-symptomatic phase, often lasting decades.

Common clinical manifestation of Atherosclerotic Vascular Disease (AVD), such as acute myocardial infarction, unstable angina, stroke or sudden cardiac death, usually occur following the rupture of a large plaque in the blood vessel wall. It is very unusual for these events to occur as part of a slow, progressive obstruction in an artery (a common misconception).

Unfortunately, modern medical practice is still quite reactive. Although there is much “lip service” given to preventative medicine, many people have inadequate management of their cardiovascular risk factors, especially at the level of primary prevention. Often, preventative medicine only begins once an event has occurred, which is counterintuitive.

This lack of effective preventative emphasis is not just the fault of the medical profession. The majority of human beings find it difficult to adopt preventative strategies demonstrated by the increasing rates of obesity, diabetes and the common rates of cardiovascular disease. Between 20 to 25% of the adult population continue to smoke and most people put little effort into effective stress management. Only a minority of society performs regular exercise.

When chronic preventative pharmaceutical agents are commenced, such as lipid lowering therapy, anti-hypertensive treatments or aspirin, only around 50% of patients remain compliant after 12 months (3-5). The saying, “it’s hard to make an asymptomatic patient feel better”, rings true. Many members of the public adopt the attitude of maintaining the current life habits, expecting the medical profession to solve their health problems once they have arisen. The new paradigm for the management of cardiovascular disease is the control and potential reversal of atherosclerosis. Fonarow (6) in a recent presentation to the Cleveland Clinic discussed three important myths regarding heart disease.

- i. Most clinical events are caused by major stenoses. Fonarow sights evidence supporting the view that the majority of acute myocardial infarctions occur over lesions which have previously been described as mild (less than 50%).
- ii. Patients with ischaemia are at higher risk – it is the atherosclerotic load and not the degree of ischaemia, which provides the greater risk. We should therefore be examining methods which detect and quantitate atherosclerosis and its manifestations (such as arterial stiffness, measurements of coronary calcification), rather than focusing on the demand for evidence of significant obstructive

coronary artery disease, which is, in reality, a very late manifestation of atherosclerosis.

- iii. Reducing ischaemia improves survival – the acute management of coronary stenoses with either an angioplasty, stenting or coronary bypass procedures is a well validated approach, but recent studies demonstrated no improvement in long-term rates of fatal and non-fatal acute myocardial infarction when, for example, angioplasty was compared with medical therapy.

CAUSES OF ATHEROSCLEROSIS

There are a few commonly held misconceptions in regard to the basic cause of atherosclerosis. All people living in an affluent society exist under a few common substrates. As the body was initially designed to be a hunter/gatherer, this prehistoric human condition was one of fluctuating feast and famine, depending on the availability of food (7).

In our modern society, we have a steady, over abundant supply of food ensuring that all (otherwise healthy) members of the community maintain plentiful nourishment. Another consistent feature of modern, affluent societies is the vast array of synthetic chemicals in small and at times significant amounts. These chemicals may present in varying sources, from the food we consume to the air we breathe, and the many chemicals used to clean and maintain our clothes, utensils etc.

Synthetic poisons are also ingested both legally and illegally. Another constant of affluent societies is stress, whether it be emotional/mental/psychologic stress or even the physical stress of inactivity or excessive activity (8).

The common thread here is the “excessive use of oxygen”. In the case of synthetic chemicals, the argument is as follows. As the body was designed to live in perfect symbiosis with nature, it is not as efficient in removing synthetic chemicals once they have been introduced to the body. Thus for these chemicals to be efficiently metabolised and excreted, it requires the use of more oxygen and energy (ATP). The “waste product” of this reaction is the generation of oxygen based free radicals. These oxidised chemicals are unstable chemicals lacking an electron. These free radicals then attack normal body structures and chemicals stealing electrons and thus returning to the more stable reduced state.

Typical structures affected are the endothelium, LDL cholesterol, DNA and the immune system. When an individual experiences stress, the body’s metabolic processes are increased, primarily mediated through the release of stress hormones (adrenaline, noradrenaline and cortisone). This increased metabolic turnover also increases oxygen use and thus the production of oxygen based free radicals. In societies whom are basically malnourished, there is not enough available LDL cholesterol to be oxidised and thus free radical damage will more commonly affect the white cells (immune system) and DNA. The average cholesterol levels in malnourished regions (for example, rural China) are between 2-2.5mmol/L. Infectious diseases, and to a lesser extent cancer, are the common causes of morbidity and mortality in these malnourished regions (9). Atherosclerosis is a rarity.

Once food becomes available and in plentiful supply, the cholesterol level rises above 3mmol/L and it

is above this level that atherosclerosis occurs. In fact in the majority of cases, people with life long cholesterol levels below 4mmol/L are rarely troubled by significant complications of atherosclerosis (10). Therefore, blood cholesterol levels are more a marker for the degree of nourishment rather than the primary cause of atherosclerosis.

It is free radical damage to LDL cholesterol and the endothelium in individuals with cholesterols above 3-4mmol/L, that is the basic root cause for atherosclerosis (11).

In predisposed individuals, atherosclerosis can begin in-utero and slowly develop over decades. The pre-symptomatic phase of atherosclerosis averages between 40-60 years, although clinical presentation seldom occurs before this time frame and commonly thereafter.

The presentation thus depends on the rates of atherosclerotic deposition in the blood vessel wall. The proposed reasons for the variable rate will be discussed later on.

PATHOPHYSIOLOGY/STAGES OF ATHEROSCLEROSIS

Thus the sequence of atherosclerosis (an ubiquitous finding in all populations with life long cholesterol levels greater than 3mmol/L) is as follows (12).

1. Free radical damage to the endothelium and LDL cholesterol. The endothelium (the largest organ in the body) has four main functions:
 - i) The endothelium acts as a single layer of cells lining every blood vessel in the body and thus a simple barrier.
 - ii) Contains vital regulatory vasoactive substances, nitric oxide and endothelin.
 - iii) Contains vital pro and anti coagulant substances.
 - iv) Regulate local inflammatory reactions.

Once this structure (endothelium) has been disrupted by free radicals and LDL has been oxidised by the same process, oxidised LDL can then cross the damaged endothelium and deposit in the sub-intimal space. The first stage of atherosclerosis is termed 'the fatty streak'. Whenever there has been a disruption of normal processes within the body, the immune system mounts a "response to injury". The immune response depends on the type of injury. For example, bacteria induce a neutrophil/antibody (humoral) B cell response, whereas a virus tends to produce cellular immunity involving the T cells.

The definition of oxidised LDL and subsequent formation of fatty streaks induces a monocyte-macrophage response, with mediation by signals from T cells. The macrophages ingest the oxidised LDL and become lipid laden, otherwise known as foam cells. As the inflammatory response intensifies, the fatty streaks evolve into a fatty plaque.

At this stage of the process, there is little or no encroachment of the lumen of the blood vessel. For decades the atherosclerotic process is basically mural and as plaque size increases there is typically a compensatory dilatation of the lumen, maintaining normal arterial flow. Often this second stage, known as the “fibrous plaque”, may involve up to 40% of the cross sectional area of the blood vessel wall, with no angiographic evidence of obstruction.

There is a common misconception that it is small plaques that often rupture to precipitate an overlying thrombus and thus an acute clinical presentation. These so called small plaques are only small from an angiographers view point but are in fact large if the entire blood vessel is considered. The common sites for fibrous plaque formation are in medium to large arteries, such as the coronaries, carotids, aorta and its larger branch vessels.

The final stage of atherosclerosis is known as the “complicated plaque” (13). This is directly related to either fibrous plaque rupture or erosion. Plaque rupture is defined as disruption of a fibrous cap on a lipid core. The lumen is separated from the underlying lipid core by a thin fibrous cap. Plaque erosion is defined as a superficial erosion in direct contact with an acute thrombus without rupture of a lipid core. The risk factors for plaque rupture are male sex, cigarette smoking and inflammation. The risk factors for erosion are prior chronic stable angina, female sex, younger with less narrowing and calcification.

Integral to the generation of the complicated plaque is thrombosis. The entity “athero-thrombosis” deserves more emphasis. One of the major contributors to the severity of the clinical presentation of plaque rupture or erosion is the degree and amount of thrombosis generated over the plaque in question.

THE ATHEROSCLEROTIC SPECTRUM

In fact, there is a spectrum between atherosclerosis with little thrombosis to athero-thrombosis with little atherosclerosis. Although uncommon, patients with a strong tendency to thrombosis may present with an acute ischaemic syndrome with only minimal evidence of atherosclerosis.

For the purpose of this discussion, I would like to introduce the “bell shaped curved” concept. All members of any community exist on a continuum between bleeding and clotting. It is, indeed, rare for a haemophiliac to suffer complicated atherosclerosis because it is so difficult for them to form a mature thrombus (14).

At the other extreme, when a patient with a distinct thrombotic disorder (eg Factor V Leiden; Anti-phospholipid antibody Syndrome etc) suffers a ruptured or eroded plaque, this markedly increases the risk for a significant large thrombus to occur over the plaque, thus increasing the severity of the clinical presentation. This is why aspirin prophylaxis (in predisposed individuals) has been so successful in preventing ischaemic syndromes by around 25%. This is precisely the proportion of people in society with a significant tendency to thrombosis (15).

Interestingly if you follow a large, unselected population of people ingesting aspirin for around 20 years, around 25 – 30 % have suffered a major bleed, again corresponding with the proportion of the opposite

end of the clotting - bleeding continuum.

Thus, assessment of thrombotic tendency using a thrombophilia screen becomes important in those patients with minimal evidence of atherosclerosis on non-invasive or invasive testing and or minimal risk factors for atherosclerosis, presenting with an acute ischaemic syndrome.

This category of patients (ie those prone to athero-thrombosis with minimal atherosclerosis) will probably not benefit from long term anti-atherosclerosis management and are better managed by anti-platelet and or anti thrombotic therapy depending on the specific hyper- coagulable disorder.

ATHERO-INFLAMMATION

Another important factor determining the rate of progression of atherosclerotic lesions and indeed the degree of plaque rupture and erosion is inflammation.

A “switching on” of the “inflammatory system” in response to either infective or non- infective antigens will increase the rate of progression of atherosclerosis and increase plaque rupture and erosion. Seminal work by Ridker and colleagues (16) has focused on highly sensitive C-reactive Protein (hsCRP) which is an excellent marker (and possible contributor) to the inflammatory potential of an individual. The prospective association of hsCRP in the higher quintile and cardiovascular risk has been shown to be more predictive than an elevated cholesterol level as a risk marker for cardiovascular disease. Recent work has shown statins, agents used to lower cholesterol, also significantly reduced CRP levels. In many ways it is difficult to separate the cholesterol lowering benefits of statins from the pleiotropic effects (ie their ability to reduce inflammation and other effects) (17).

The proposed mechanisms are an increased systemic inflammatory response, also increasing local inflammatory reactions especially at local sites of damage, such as arterial wall lipid accumulation. Thus, the full blown atherosclerotic response is, in many ways, a healing response to the initial injury of free radical associated lipid deposition in the arterial wall.

The increasing inflammation (ie deposition of varying white cells and other inflammatory mediators) eventually weakens the fatty plaque. Rupture of the plaque usually occurs at the shoulder of a plaque, the area of greatest concentration of inflammatory cells. A family of enzymes, known as metalloproteinases, produced within the blood vessel wall, also increase the risk for plaque rupture and thinning of the fibrous cap over the plaque (18).

An increasingly discussed infective association is that of the chronic respiratory organism Chlamydia. A prior infection with Chlamydia has been associated with high rates of clinical cardiovascular events and complications following an acute event. Chlamydial inclusion bodies have been found in atherosclerotic plaques at autopsy and in arthrocentesis specimens prompting some researchers to suggest this is almost a ubiquitous finding (19). At this stage, however, there is speculation as to whether varying antibiotic regimens to treat Chlamydia are having an impact on the atherosclerotic process. More work needs to be done in this area.

RISK FACTORS

Risk factors represent associations that may or may not be causative. Although, cardiovascular disease occurs in people without risk factors, it is more likely to occur in those with risk factors present. The best definition of a risk factor is the presence of a factor associated with an increased likelihood that disease will develop at a later stage. There are a variety of clinical and investigational-based risk factors which vary in their degree of association (20)

Some risk factors are modifiable (for example cigarettes, hypertension, lipids) whilst others are non-modifiable (for example age, sex and family history).

The three major points to consider regarding risk factors are as follows:

1. A valid statistical association – once chance, bias and confounding explanations have been excluded.
2. A cause and effect relationship from:
 - a. The totality of evidence – not one study;
 - b. The strength of association;
 - c. The temporal sequence;
 - d. The dose response;
 - e. The consistency of evidence;
 - f. Biologic plausibility;
 - g. The specificity.
3. Measurement of risk in relative or absolute terms.

Non-Modifiable Risk Factors

These include Age, Sex and Family History.

- a) Age - As atherosclerosis occasionally occurs in utero, it can be considered (in most cases), a life-long disease. As it is (without intervention of some sort), slowly progressive, it is therefore logical and evidence-based to state that the risk of clinical cardiovascular events increases with age (21).
- b) Sex – In women, cardiovascular events occur, on average, at least 10 years later than men. In fact, cardiovascular events are unusual in women prior to menopause. Until recently, it was thought that oestrogen was protective but recent work from the Heart Institute in Sydney has shown that it is more likely to be the deleterious effects of testosterone that induce progressive atherosclerosis in men before the relative increase in androgen levels seen in women after menopause (22-23).
- c) Family History – The vague notion of family history as a non-modifiable risk factor is probably incorrect in most cases. So-called “genetic” inheritance of cardiovascular disease is

more specifically an inherited risk factor such as a particular lipid disorder, a tendency to diabetes, hypertension or thrombosis. It is, therefore, more appropriate to search for the specific, familial tendency and specifically attempt to modify the risk factor or combination of risk factors to then, hopefully, modify the natural history of their condition.

Modifiable Risk Factors

The modifiable risk factors can be grouped as follows:

- a) Lipids;
- b) Cigarette smoking;
- c) Diabetes;
- d) Homocysteine;
- e) Thrombotic tendency;
- f) Inflammation

a) Lipids

1. Cholesterol – since the landmark work of Ancel Keys commencing in the 1950's (24) hypercholesterolaemia has become the major “popular” association with cardiovascular disease. There is, however, an ongoing debate regarding the true importance of cholesterol in occupying this central position. I believe the totality of evidence supports single and/or combined lipid abnormalities as central to the development of cardiovascular disease but it is too simplistic to purely focus on cholesterol levels. The association between cardiovascular events and lipid abnormalities is, however, quite straightforward.
2. LDL – the major sub-factions of total cholesterol are LDL (the bad cholesterol) and HDL (the good cholesterol). LDL (Low Density lipoprotein) is the lipid transport protein which delivers LDL cholesterol to the tissues. There is a large body of work discussing oxidative modification of LDL, which is the key step in the initiation and growth of fatty plaques (25) Measurement of ApoB (an important protein contained in the outer layer of LDL cholesterol) may add to the specificity of LDL effect, although its additive benefits as a synergistic pointer to cardiovascular events remains in question (26).
3. Seminal work from Professors Ron Krauss and Robert Superco from Berkeley, California, has analysed sub-factions of LDL. Their group has published numerous papers demonstrating a consistent association of small, dense LDL (pattern B) compared with large, buoyant LDL (pattern A) and cardiovascular events (27). Interestingly, one of these studies demonstrated an increase in pattern B LDL with reducing amounts of dietary fat. This evidence is part of the increasing trend against the long-held belief of the benefits of a low fat diet (28).
4. LDL – There are numerous studies demonstrating the cardio-protective benefits of an elevated HDL (greater in 60mg/decilitre, greater than 1.3 mmoles/litre). The total cholesterol to HDL ratio offers a much more specific marker for cholesterol events compared with total cholesterol alone.

Cholesterol

HDL > than 4.5 suggests high risk

Cholesterol

HDL < than 3.5 is acceptable.

Cholesterol

HDL < than 2.5 is ideal

ApoA1 is the major lipoprotein carrying HDL1 which is felt to be the most cardio-protective HDL. It is still uncertain whether measurement of ApoA1 confers more information than measurement of HDL alone.

5. Triglycerides – triglycerides are the lipid component intricately linked to dietary fat and carbohydrate. There is an inverse relationship between blood triglyceride levels and HDL cholesterol. Therefore, there is an ongoing dispute as to whether the risk from an elevated triglyceride is because of the associated low HDL or is an independent risk factor in itself. Regardless, when the Helsinki Heart Study data was re-analysed, a combination of cholesterol/HDL greater than five and triglyceride greater than 2.3 mmol/litre demonstrated a marked increase in cardiovascular events (29).
6. Lp(a)- Lipoprotein (a) is a large molecule characterised by a LDL linked to a protein designated Apo(a) which bears a striking homology with plasminogen without the biologic action. Thus, Lp(a), promotes fatty plaques and increases the tendency to thrombogenicity. Around 20% of the population has elevated levels of Lp(a) (greater than 30mg per decilitre). Numerous perspective studies have demonstrated around a 70% increase in cardiovascular risk in this group.

b) Cigarette smoking

Cigarette smoking doubles the risk of coronary heart disease and approximately 30% of coronary heart disease deaths are attributable to cigarette smoking. This relationship is in a dose-related manner. Cigarette smoking increases all cause mortality rates by around 60%. Recent data from the USA suggested the risk of cardiovascular death was also around 60% higher in passive smokers when compared to non-smokers (30). Interestingly, there is a rapid decline in mortality rates within months of smoking cessation, regardless of age and length of smoking.

c) Diabetes

Both forms of diabetes (insulin-dependent diabetes and non-insulin-dependent diabetes) are associated with marked increases in cardiovascular morbidity and mortality (31). Establish NIDDM carries the same cardiovascular risk as angina pectoris and therefore should be managed aggressively. Although there is a link between glycaemic control and cardiovascular risk, there are numerous other associations with diabetes that independently contribute to cardiovascular event rates.

The basic pathogenesis of NIDDM is insulin resistance. The insulin resistance syndrome (which is present in approximately 30% of Caucasians, 50-60% of Asians and close to 100% of “black races”) is associated

with the following five clinical scenarios.

- a. NIDDM;
- b. Hypertension;
- c. Dyslipidaemia – the classic lipid abnormalities seen in the insulin resistance syndrome are:
 - i. A normal to modest elevation in total cholesterol;
 - ii. A moderate to significant elevation in triglycerides;
 - iii. A low HDL cholesterol.
- d. Abdominal obesity;
- e. Cardiovascular disease.

Therefore, optimum management of diabetes addresses targeted, aggressive management of each separate issue. For example, management of glycemic control will have little effect on hypertension, dyslipidaemia or abdominal obesity.

d) Homocysteine

Homocysteine is a toxic amino acid formed from the essential amino acid, methionine. There are numerous reasons for elevated levels of homocysteine in the bloodstream ranging from severe genetic disorders to poor lifestyle. End stage renal disease is commonly associated with elevated homocysteine levels which compounds the vascular complications of the renal disease itself. The first line of defence against oxygen-based free radicals is the endogenous and exogenous antioxidant system. When free radicals penetrate this system, damage to normal body structures ensues. The re-methylation of these structures assists in repair. Homocysteine levels are an indirect indication of the efficacy of methylation (32). There are now numerous studies of linking elevated levels of homocysteine and cardiovascular risk. There are, however, conflicting studies of therapeutic interventions to reduce homocysteine and a subsequent decrease in cardiovascular risk (33). The mainstay of treatment of moderate elevations of homocysteine (greater than 10 micromoles per litre) are the B group vitamins and, in particular, folic acid, B6 and B12.

e) Thrombotic Tendency

As discussed, atherothrombosis is an extremely common component of acute cardiovascular events. A tendency to thrombosis, however, is not just a vague, non-specific tendency to clotting but is usually a specific clotting disorder that requires targeted treatment. In patients, where there is a strong suspicion of a thrombotic disorder, an appropriate blood screen should be performed.

f) Inflammation

Atherosclerotic vascular disease is not simply the progressive accumulation of fat in the arterial wall, culminating eventually in rupture or erosion into the lumen by mechanical forces. Inflammatory cells and proteins also play a key role in the entire process. T-cells, macrophages and numerous inflammatory mediators are prominent features of the atherosclerotic process occurring from the initial endothelial

dysfunction – fatty streak stage, to the clinical presentation of acute vascular events (34).

Infection

Over the last decade, there has been an increasing emphasis on the contribution of infective organisms in the generation, progression and acceleration of atherosclerosis. Chronic infection with Cytomegalovirus and Helicobacter has been linked to atherosclerosis, but most of the evidence is related to Chlamydia Pneumoniae (35). Chlamydia Pneumoniae is an intracellular atypical bacterium which comprises around 10-15% of community acquired pneumonia. Although the rates of abnormal titres to Chlamydia Pneumoniae in patients with acute vascular events is quite low, Chlamydia Pneumoniae is found by immunofluorescence staining in around 80% of autopsy or atherectomy derived atherosclerotic plaques (36).

The question still remains as to whether Chlamydia Pneumoniae is a causative or commensural organism. The studies of antibiotic therapy directed against Chlamydia Pneumoniae in patients with acute vascular events is also conflicting. Recently, there has been evidence to suggest that current bacteriostatic antibiotic therapy used (eg azithromycin) is not adequate to eliminate the organism and therefore longer and different treatment schedules may need to be used to completely eradicate this infection. At present, further studies need to be performed before antibiotic therapy becomes a suggested treatment for prevention and treatment of atherosclerosis (37).

PREVENTATIVE SCREENING

There is much lip service from politicians and health professionals as to the value of preventative medicine, with bodies such as the National Heart Foundation of Australia and the American Heart Association, lauding the benefits of lowering cholesterol and regular exercise.

In reality, however, there is little effort at the “coal face” in moving from a reactive “disease based”, so-called health care system to a pro-active preventative system. I believe, the major reason for this is human nature. We are all more geared to the “quick fix solution” rather than putting in the “hard yards” to seek and achieve long term goals.

Preventative medicine, which includes preventative screening, is a “hard sell”. It is difficult to make an asymptomatic person feel better and thus the majority of people in society prefer to deal with the acute issues of the day rather than considering the possible consequences for the future.

The instant gratification mantra has been the standard for the past 25-30 years, seen obviously in modern advertising, accepted credit card debts and the increasing relationship breakdowns devastating many families. For us at a societal and personal level to improve the quality of our lives, we need to improve the quality of our health. This can only be achieved through an integrated preventative program, the first step of which is a comprehensive, accurate screening assessment to determine the current level of risk for disease.

As cardiovascular disease is the major cause of morbidity and mortality in modern society, accurate cardiovascular screening must be the cornerstone of a preventative screening program.

The next question is, when should screening start? The obvious answer to this is it depends on the individual risk and on the particular test. As the earliest pathologic manifestations of atherosclerosis occur at a very early age, the timing of screening programs becomes crucial. On one hand, screening with a low cost, simple risk algorithm is a useful population screening tool with the more sophisticated, expensive methods being reserved for intermediate to higher risk groups. As autopsy studies clearly show the very high incidence of significant atherosclerosis in young people (less than 30), many representative medical bodies are suggesting simple screening at an early age.

For example, a simple questionnaire administered during a routine doctor's visit or consultation with other health professionals in all adults could easily and accurately identify higher risk individuals. Until recently it was felt that only 50% of individuals with proven clinical atherosclerotic coronary artery disease had one of the major risk factors.

Two recent large scale population studies (38-39), however, disagree with this conventional wisdom, suggesting the vast majority of patients suffering a vascular event have a major risk factor for atherosclerotic disease (AVD). There are, however, a number of individuals with one or more major risk factors for AVD who will never suffer a clinical event in their life time and therefore may undergo years of unnecessary treatment or be unduly worried by the particular risk factor.

The major risk factors for AVD are:

- i. High cholesterol.
- ii. Hypertension.
- iii. Cigarette smoking.
- iv. Diabetes or a history of glucose intolerance.
- v. Family history of AVD before the age of 55 years old.

Therefore, a basic questionnaire covering each of these areas is a simple, inexpensive method for identifying those at risk. It is obviously more cost effective to target more sophisticated health screening rather than encouraging all adults to participate in regular programs.

SCREENING CRITERIA

In an ideal world with no cost restraints, the least invasive, most accurate screening assessment should be offered to all those at risk of the disease. This screening test should therefore satisfy the following criteria:

- The underlying disease to be screened for has a long asymptomatic phase. AVD fits this criteria.
- The screening test has general acceptance within the scientific community with associated, appropriate randomised clinical trial data to support its use.
- By detecting the disease early, the quality and quantity of life will be positively altered.
- The interventions suggested based on the results of the screening test are safe and effective. The benefits of these interventions should outweigh the known long term side effects of treatment. The incidence of side effects should be considerably less than the consequences of the untreated underlying disease process.
- The procedures should be easily performed (including not time consuming) and inexpensive.
- The population screens should comply with the advice and the intervention suggested.
- The prevalence and seriousness of the disease justifies the cost of screening and treatment.
- The suggested treatment to prevent the manifestations of the disease is acceptable and efficacious.

In our modern, real world where cost restraints are important, the following extra points need to be considered:

a. Is the screening method and subsequent treatment program cost effective?

For example, a screening program may be self-funded, corporate sponsored or community based and thus paid for by the tax payer.

Once a high risk person is identified, the cost of subsequent investigations and the treatment that follows is almost always paid for mainly by the existing health care system.

For example, let us consider the following situation.

A 45 year old male attends a CT scanning clinic for a CT of his coronary arteries following reading an advertisement in a newspaper for this technique. His father died at 52 of a heart attack and recently he has experienced some minor chest pain during exertion.

He pays for the test and has a coronary calcium score of 480, which places him in a high risk group. It is suggested by the CT clinic he obtains a referral to a cardiologist for further assessment and he undergoes stress imaging with echocardiography. This suggests anterior wall ischaemia and coronary angiography is

subsequently performed.

A tight LAD lesion necessitates coronary stenting and the cardiologist suggests usual care, aggressive risk factor modification.

Without the screening test, this person may have entered the medical system via more conventional means but there is no doubt many more people will be detected at earlier stages of their “vascular career” and commence investigations and treatment at an earlier stage, thus burdening the health care system further.

Some clever statistician needs to determine the difference between the costs of early disease detection and subsequent management versus conventional treatment of those presenting with either acute or chronic systems. This needs to be balanced against the chronic management of heart failure and the economic and emotional aspects of severe debilitating chronic disease and cardiac death.

b. Can our Current Health Care System cope with the extra cost and burden of screening?

Most modern health care systems are already stretched to the limit with long waiting lists, staff problems and limited funding, let alone the extra burden of detecting early presentation of the disease and the subsequent management necessary.

During 1999 Sydney Heart Image commenced a cardiac screening service utilising CT scanning of the coronary arteries. Of the 20,000 patients screened, only 10% required further cardiologic investigations and of those only 10% (1% of the entire cohort) progressed to coronary angiography (hardly a drain on the health care system)!

All of those requiring coronary geography demonstrated significant obstructive coronary artery disease, the majority requiring some form of coronary intervention (PTCA or CABG). This particular form of screening is to be compared with the incredible burden on the health care system of patients with minimal risk factors for coronary disease but atypical chest pain and equivocal stress ECG proceeding to coronary angiography. In this situation around 50% of the angiograms are entirely normal and should not have been performed in the first place. More accurate screening methods such as CT scanning of coronaries, arterial screening using applanation tonometry or even stress echocardiography could have markedly reduced the need for these unnecessary procedures.

It is my opinion, more sophisticated screening techniques should be offered to targeted groups. These groups should be based on:

- i. Age.
- ii. Sex.
- iii. Level of risk based on standard risk factors.

ARTERIAL STIFFNESS

Atherosclerosis is the underlying primary cause for acute or chronic ischaemic syndromes in the vast majority of cases. There are numerous contributing factors to the generation of atherosclerosis despite the end result being the same basic process.

Since Framingham and numerous other corroborative studies have confirmed the importance of screening for atherosclerotic risk factors, there has been a relatively recent push to screen for atherosclerosis itself. There are numerous invasive and non-invasive investigations that offer an estimate for the presence and degree of atherosclerosis (40-41).

As atherosclerosis is a mural disease for decades prior to encroachment of the lumen, techniques focusing on the arterial wall are becoming of increasing interest to the medical/scientific community. A major player in this area is assessment of arterial stiffness. Stiffness is a general term describing resistance to deformation (42). Arterial stiffness occurs in all societies in direct relation to age. Conditions such as atherosclerosis and hypertension accelerate the degree of arterial stiffness. Arterial stiffness is therefore not specific for atherosclerosis but is now well established as a cardiovascular risk factor (43).

There is also a strong relationship between arterial stiffness and cardiovascular risk factors. In populations with a history of one or a combination of the major risk factors, there is direct and indirect evidence of graded arterial stiffness (44).

There are however still some questions in regard to arterial stiffness.

- a. Is arterial stiffness a marker for cardiovascular risk and/or directly involved in the pathologic process?
- b. Is arterial stiffness or its preponderance to cause an increased pulse pressure both at a central and systemic level, the major factor in contributing to cardiovascular risk?
- c. Is arterial stiffness a marker for occult atheroma, endothelial dysfunction or in itself a direct cause of atheroma?
- d. Is it enough to target only systolic and diastolic blood pressure, along with peripheral pulse pressure, or does arterial stiffness measurements give more information, allowing better risk stratification?

DEFINITIONS

Arterial stiffness

General term describing resistance to deformation.

Compliance

Change in the geometry (usually area but can also include volume, diameter etc) per change in pressure.

Distensibility

Percentage change in area per change in pressure.

Elasticity

Measure of stiffness. Change in wall stress for a given change in strain. Stress equals force per unit area - strain equals ratio of change in the area compared with the initial area.

ARTERIAL STIFFNESS

Pathophysiology

According to the Windkessel Theory, the heart pumps blood directly into the aorta and thence into the large arteries. These large arteries, in the normal state, are high in the protein, elastin and thus create a central elastic reservoir. Blood then travels into the peripheral smaller more muscular arteries, with less elastin and more collagen, which are relatively inelastic conduits (45).

Elasticity depends directly on the distending pressure. As the distending pressure increases, this leads to greater recruitment of the relatively inelastic collagen fibres and thus, decreased elasticity. Distending pressure is determined by the following factors:

1. Mean arterial pressure (most important).
2. Endothelial function.
3. Arterial wall smooth muscle bulk and tone.

Diastolic pressure gradually increases to middle age then usually declines. This is thought to be due to slowly progressive changes in the muscular peripheral arteries leading to increased arteriolar tone.

As the large arteries lose their elastin and become stiffer with age, there is a progressive rise in systolic blood pressure. Apart from the increase in arterial stiffness, there are two other factors thought to be important in this process.

1. Peripheral pulse wave reflection.
2. Pattern of LV ejection.

Pulse Wave Reflection

This is an important component of systolic hypertension. In the normal, young adult without hypertension, a wave is propagated throughout the arterial system with each heartbeat. In young, elastic large arteries,

there is normal distensibility and a slower forward wave. When this normal wave arrives at the smaller muscular arteries, a reflected wave travels back to the heart. This slow reflection means the reflected wave will arrive back to the proximal aorta leading to an augmentation of coronary blood flow during diastole, ie an important physiological phenomenon leading to efficient coronary blood flow.

With age and subsequent pathophysiologic arterial stiffness, the forward wave is propagated faster through the less compliant (stiffer) larger arteries thus arriving at the distal arteries earlier with rapid reflection back to the central circulation usually around late systole. This lack of diastolic augmentation leads to reduced coronary blood flow. The systolic augmentation contributes to systolic hypertension.

The combination of increase in systolic blood pressure and decrease in diastolic blood pressure leads to a significant increase in pulse pressure.

Pattern of LV Ejection

The reduction in coronary blood flow and increased systolic blood pressure lead to the following consequences:

- Diastolic dysfunction reduces coronary filling and thus decreases cardiac function.
- LV stiffness - the combination of increased systolic blood pressure and decreased coronary blood flow, stiffen the left ventricle leading to left ventricular hypertrophy. Left ventricular hypertrophy and other pathophysiologic circulatory changes create a vicious cycle compounding all of the above problems.
- The reduced augmentation of the diastolic reflected pressure wave leads to reduced diastolic blood pressure. This leads to a widened pulse pressure. The normal pulse wave velocity is 5-10 metres per second. In young subjects (less than 50 years old), diastolic blood pressure is a better predictor of future cardiovascular events. In older subjects, systolic blood pressure and pulse pressure are better predictors.

In those less than 50 years old, increased diastolic blood pressure leads to increased early wave reflection and thus further augmentation of diastolic blood pressure and therefore decreased pulse pressure amplification.

In those greater than 50 years old - arterial stiffness leads to systolic amplification and therefore increased systolic blood pressure, decreased diastolic blood pressure and thus increased pulse pressure. An increase in arterial stiffness and wave reflection amplitude lead to a marked increase in systolic and pulse pressure. (There is also a slight decrease in the diastolic and mean arterial pressure as the wave travels towards the periphery). The components of systolic and pulse pressure are greater in the periphery compared with the ascending aorta. The degree of amplification is related to the difference between the elastic moduli of the respective arteries and the distance to reflection sites. Therefore brachial pulse pressure is not always an accurate reflection of the central (ascending aortic) pulse pressure. The estimation of central pulse pressure is closely related to left ventricular afterload and left

ventricular mass, which has been shown to be an independent predictor of heart failure and coronary heart disease mortality.

Numerous studies have confirmed that central arterial pulse pressure is a better predictor than brachial pulse pressure of:

- i. Carotid intimal-medial thickness.
- ii. Post PTCA restenosis.
- iii. Coronary artery disease severity.
- iv. Mortality in end stage renal failure.

The systemic arterial system delivers blood at high pressures to the periphery. It can be divided into three separate anatomic regions with distinct and separate functions (46).

- i. Large arteries - aortic, carotid, iliac - buffering reservoir - stores blood during systole and expels to periphery during diastole ensuring steady flow to capillaries and tissues throughout the entire cardiac cycle.
- ii. Muscular arteries - (especially lower body, femoral, popliteal, posterior tibial - twice as long as elastic arteries). They alter smooth muscle tone and modify the speed of travel of the pressure wave along their length and determine the speed of the reflected waves.
- iii. Arterioles - alter peripheral resistance and therefore maintain mean arterial blood pressure.

At low levels of pressure, the wall stress is supported by compliant elastic fibres, but at higher pressures, wall stress is supported by the stiffer collagen fibres.

With increasing age, systemic arteries undergo a change independent of atherosclerosis. The intima undergoes hyperplasia. The medial elastic fibres and laminae display thinning, splitting, fraying and fragmentation. The age related elastin and collagen changes are not seen in the muscular arteries.

Collagen in the human aorta is 500 times stiffer than elastin. Collagen doubles in content from the age of 20 to 70. Arteriolar density decreases secondary to vascular rarefaction secondary to atrophy from age. The changes in the elastic arteries and arterioles lead to increased stiffness and resistance, but the stiffness is more than the resistance.

METHODS FOR MEASURING ARTERIAL STIFFNESS

There are three broad groups of non-invasive assessment of arterial stiffness.

- i. Measurement of pulse wave velocity.
- ii. Relating diameter (or area) change of an artery to distending pressure.
- iii. Assessing arterial pressure wave forms.

i. Pulse Wave Velocity

This is a simple measurement and the velocity of arterial wave propagation is closely related to arterial stiffness. The typical method of measuring pulse wave velocity is to record the arterial pulse proximally (common carotid artery) and more distally (femoral artery) and determine the time delay either by simultaneous measurement or gating the R wave of the electrocardiogram (47). Other methods of estimation of pulse wave velocity include pressure sensitive transducers, Doppler ultrasound, Applanation Tonometry and MRI. The normal pulse wave velocity ranges from between 5-10 metres per second (48). Increased pulse wave velocity occurs with:

- Increasing the distending pressure. Therefore blood pressure must be recorded at the time of measurement.
- Increasing the heart rate - one study suggested increasing the heart rate by 40 beats per minute leads to a 1 metre per second increase in pulse wave velocity.
- Established cardiovascular risk factors - age, hyperlipidaemia, non-insulin dependent diabetes, sedentary life style etc.

The odds ratio for a 5 metre per second increase pulse wave velocity is 1.34 for all cause mortality and 1.51 for cardiovascular mortality. In the Laurent study, pulse wave velocity was more accurate in predicting cardiovascular mortality than assessment of peripheral pulse pressure.

ii. Relating change in vessel diameter (or area) to distending pressure.

Ultrasound, especially of the carotid artery, is the most commonly employed method to assess arterial stiffness from considering change in vessel diameter and distending pressure. An excellent explanation of this technique is found in the article by Oliver and Webb (45)

iii. Assessing arterial pressure wave forms - Pulse wave contour Analysis (PWCA)

Augmentation - Assessment of pulse wave velocity focuses on forward flow. The “backward” reflected wave is also an important component of propagation of flow throughout the arterial tree. This reflected wave augments the pressure centrally, depending on the timing of the reflected wave and now can be measured either invasively or non-invasively as an augmentation point. The augmentation point is defined as the first visible or measured inflection point on the composite arterial wave form (47). The

location and timing of the augmentation point depends on the following factors:

- i. Distance to the reflection site - determined by the size of the individual.
- ii. Amplitude of reflection.
- iii. Pulse wave velocity at the site - which depends on the degree of arterial stiffness and the diameter of the arteries involved.

The augmentation pressure equals the maximal systolic pressure minus the pressure at the inflection point.

It is important to note that by convention, when the augmentation point occurs after the peak of pressure, it is given a negative designation. The augmentation index is the augmentation point expressed as a percentage of the pulse pressure. Augmentation index equals brachial systolic pressure minus pressure at augmentation point divided by pulse pressure expressed as a percentage normal range plus 80% to minus 30%.

The closer to the beginning of systole, the stiffer the arteries and the larger the percentage. The closer to diastole, the more elastic the arteries and thus the more negative the result. The greater the augmentation index, the greater the degree of arterial stiffness. Augmentation index is dependent on:

- i. The timing of the reflected wave, which is determined by gender, height, reflection amplitude and stiffness.
- ii. The shape of the forward wave which is determined by the left ventricular outflow and ascending aortic elasticity. Two important variables of augmentation index are height and pulse rate. There is an inverse relationship between augmentation index and height and an inverse relationship between heart rate and augmentation index. An increase in heart rate of 10 beats will reduce the absolute augmentation index by around 4-5% (49). Therefore short, bradycardic people will have a falsely high augmentation index and short bradycardic females will have an extremely high augmentation index which may not accurately reflect the degree of stiffness of their arteries.

ARTERIAL STIFFNESS AND PROGNOSIS

Despite the robust nature of simple coronary risk scores (eg Framingham, ESC, Smart, EPOZ), there are many patients within low, medium and high-risk scores who fall outside the predicted levels of risk. Therefore a number of people are over-treated, under-treated, falsely concerned and falsely reassured. Therefore simple inexpensive screening tests which add value to coronary risk evaluation need further investigation.

The most promising additional parameter is the emerging and well-validated technique of arterial

screening assessing stiffness using a number of different methods.

For many years there has been a well-established relationship between the level of blood pressure and cardiovascular risk (50). Numerous studies have confirmed this relationship. In recent times, however, there is emerging strong evidence that systolic, diastolic, mean and pulse pressures measured at the brachial artery are not always strong and accurate measures of cardiovascular status and risk in varying risk groups (51).

With the availability of highly accurate non-invasive measures of central and peripheral arterial stiffness, many studies are now demonstrating a greater predictive accuracy for future cardiovascular risk (52-57). Thus it is logical these non-invasive techniques may be incorporated into existing risk factor assessment to increase the overall predictive accuracy of screening.

The advent of calcium scoring using multi-slice, high-speed CT scanners or EBCT, has added predictive value to current, basic risk factor assessment such as the Framingham risk factor analysis (58-60). Although CT scanning provides an accurate assessment of atherosclerotic load, it remains controversial for reasons including radiation dose, cost effectiveness and the robustness of follow up scan data (61-62).

Non-invasive measures of arterial stiffness, such as applanation tonometry, offer an inexpensive, accurate, reproducible measure of atherosclerotic risk in varying risk groups without the radiation concern and expense of CT, both to the operators and the consumer (63). Although there are now numerous studies of arterial stiffness (using various techniques) and long-term vascular risk, in varying higher risk groups, there is limited information at present as to its validity as a prognostic indicator in lower risk groups. At present there are four ongoing studies (ASCOT, SEARCH, FIELD AND MESA) which should shed light on this issue (64-67). For any study in low risk groups to have adequate power it must include large numbers and continue for a long time course (at least 10 years). The MESA study of multiple screening techniques will certainly answer many questions in relation to these matters

As vascular disease remains the major cause of morbidity and mortality in modern society and has an extremely prolonged pre-symptomatic phase, it is logical early detection, risk factor stratification and preventative management is the correct approach.

Thus the more information available for each individual's risk, will allow the most appropriate use of medical resources and lead to a long term reduction in the carnage from vascular disease. Professor Michael O'Rourke from Sydney's St Vincent's Hospital pioneered the assessment of the arterial pulse a number of years ago. He has since developed the technique of applanation tonometry using a 3mm pencil probe positioned over a selected artery (usually radial or carotid) utilising a piezo-electric crystal which analyses the contour of each pulse wave. This compliance or stiffness measure using the SphygmoCor system allows an accurate measure of peripheral and extrapolated central compliance. The central measures have been well validated using a transfer function to within a few percent of central arterial catheters (68). There have now been multiple papers demonstrating the predictive value of non-invasive arterial compliance measures. The majority of papers have been in the hypertensive population but other high-risk groups have also been assessed.

Laurent et al (69) studied 1980 hypertensive patients for an average follow up of 112 months. During this time there were 107 fatal and 46 cardiovascular deaths. Pulse wave velocity was significantly associated with fatal events. For each 5metre/ second increase in pulse wave velocity there was a 2.14 and 2.35 (respective) odds ratio. The conclusion from the study was pulse wave velocity (a direct measure of arterial compliance) was an independent risk factor for cardiovascular events. It was an independent predictor of all cause and cardiovascular mortality independent of previous cardiovascular disease, age and diabetes. By contrast, the peripheral pulse pressure was not significantly and independently associated to mortality. This study provides the first direct evidence that aortic stiffness is an independent predictor of all cause and cardiovascular mortality in patients with essential hypertension.

Patients with either proven vascular disease or strong risk factors have been clearly shown to have stiffer aortas. A study by Lehmann et al demonstrated an inverse relationship between severity of risk and aortic compliance (70).

PREDICTIVE VALUE OF ARTERIAL STIFFNESS

When considering the predictive value of arterial stiffness it is important to define the intended risk groups involved.

- i. General population - for arterial stiffness to be adopted as a screen in the general population, it should provide additional prognostic information over traditional risk factor analysis. To date, this data is not available but should be answered with the results of four trials currently in progress (64-67). As arterial stiffness is not expensive, is reproducible and does not involve radiation, it is an attractive addition to basic risk factor assessment.

Although there is ongoing criticism of cardiovascular screening techniques by many conservative members of the profession (71) the majority of people attending for an assessment have strong indications, rather than purely being “the worried well”.

At Sydney Heart Image over a 3 year period, we screened approximately 20,000 people using the technique of CT scanning of the coronary arteries. 90% of those screened had a major risk factor for vascular disease and requested an accurate assessment of their degree of atherosclerosis (unpublished data).

It is my unsubstantiated belief, arterial screening is a useful adjunct to clinical and blood pathology testing to determine true vascular risk in lower risk populations. Numerous studies to confirm this opinion are now in progress.

- ii. High risk groups - as arterial pressure is a central determining aspect of arterial stiffness, the majority of studies using this technique have been performed on the hypertensive population. There have, however, been a number of studies performed in other, at risk groups demonstrating a close relationship between the level of risk and the “stiffness” parameters. There appears to be a gradation (with additive information) between the predictive value of the simpler measure of blood pressure and pulse pressure to pulse wave velocity and augmentation index, using various methods.

Patients with the following risk factors or belonging to a specific group have been studied with the majority of these studies confirming the additive prognostic value of arterial stiffness independent of the risk itself (72-103).

- i. Hypertension
- ii. Hyperlipidaemia
- iii. Cigarette smoking
- iv. Diabetes
- v. Renal disease
- vi. Pre-existing vascular disease
- vii. Elderly, gender differences

The value of arterial screening in the subgroup of patients with existing vascular disease is in relation to monitoring the response to intervention. There are numerous studies assessing the improvements in arterial stiffness with drug therapy (104-136).

As arterial stiffness measurements have been shown to be reproducible (63), inexpensive and do not involve radiation, it will almost certainly become a standard for, not only assessing long term responses to drug therapy, but also lifestyle and anti-oxidant supplement intervention.

ENDOTHELIAL FUNCTION

Endothelial dysfunction is an essential component of atherosclerosis. Many researchers believe it is the first change in early atherosclerosis. Thus early detection and assessment of endothelial dysfunction can now allow a more targeted intervention to assist in the prevention of clinical vascular disease. Until recently, endothelial function could only be measured invasively via a cumbersome non-invasive technique involving brachial reactivity using high resolution ultrasound. In a recent paper, Wilkinson et al demonstrated a simpler, more direct method to assess endothelial dysfunction, using pulse wave analysis (137).

CARDIAC REVERSAL PROGRAM

A common misconception amongst the public is the notion that coronary artery bypass grafting has a “use by” date of somewhere between 5 to 8 years. It is, however, not uncommon for graft atherosclerosis to become clinically manifest during this time course.

Recurrence of atherosclerosis is not inevitable but is more related to the concept adopted by the patient that coronary artery bypass grafting is a curative therapy for atherosclerosis. This is of course, not the case, the operation having no effect on the underlying disease process.

Atherosclerosis is a systemic arterial disease and local therapy eg coronary artery bypass grafting, stenting etc, does not affect the systemic process. It is logical and now proven with a number of studies (138) that the disease can be slowed, arrested and in some cases reversed (139).

The most important aspect of any reversal program is to establish the major contributors/causal factors in the process and aggressively treat these factors. There are a number of accepted interventions which have been clearly demonstrated to be of benefit (140). There are also some more controversial therapies that are hotly debated in the scientific world.

In most areas of science you will always find a few dissenters, so I'll try to present both sides of the debate.

The reversal program is as follows -

1. Lifestyle modification

Despite the consensus regarding the benefits of a sensible lifestyle approach, affluent societies appear to find this the most difficult aspect of the therapy (141). For whatever reason, (an acute event, death of a close friend/relative, life changing experience), it is human nature that, following the commencement of a lifestyle program, a significant proportion of people will fall back into their old habits - regaining weight, recommence smoking and other poor life habits.

For the reversal program to be effective, lifestyle modification must be the foundation of therapy.

Lifestyle modification should involve the following steps -

- a. Correct nutritional approach - involving achieving ideal body weight, appropriate degree of caloric restriction and appropriate eating plan to suit the individual's metabolic needs.
- b. A supervised exercise and movement program.
- c. Immediate and permanent smoking cessation.
- d. Sensible or no alcohol consumption. Screening for and treating other addictive states.
- e. Individualised stress management program.

Over the recent years there has been a trend towards the use of personal trainers and life coaches. Having some type of "coach" to assist in maintaining these important strategies has been shown to increase the chance of successful maintenance of the program.

2. Nutritional supplementation

This area is controversial with many researchers in the field believing there is no value in the use of vitamins and other nutritional supplements (142) whilst others afford the concept stronger support (143).

To date, I believe the randomised, control trials have been poorly designed and the neutral and at times negative conclusions from these trials are more a reflection of trial design rather than lack of efficacy or detriment from treatment.

I believe, over the age of 35, all people should be supplementing with the following -

- a. High quality multivitamin, multimineral preparation containing at least 400 micrograms of folic acid. Dosage suggestion - one pill in the morning.
- b. Some form of Omega 3, either fish or flaxseed oil. Dosage suggestion - 1000 milligrams twice daily.

Thereafter, it is my opinion (not shared by the majority of the conservative medical world), that further supplementation should be targeted to the specific factors contributing to the atherosclerotic process (eg. lipoprotein a, homocysteine etc mentioned earlier) (144).

3. Lipid Management

The strongest evidence for reversal of atherosclerosis comes from trials involving cholesterol-lowering therapy. Interestingly, there is a group entitled THINCS who refute the cholesterol hypothesis (145).

Professor Greg Brown's group from Seattle has the strongest evidence for atherosclerotic reversal using combined (Statin and Niacin) cholesterol-lowering therapy (146). The recent REVERSAL trial (139) from the Cleveland Clinic demonstrated arresting of the disease with a dose of Atorvastatin 80mg daily over an 18 month period, compared with a 2.7% progression in the control group given Pravastatin 40mg daily.

I believe it is vital (through appropriate measurement and assessment) to target and treat the specific lipid abnormality moving the focus away from treating "cholesterol" levels.

Many researchers now believe that we should be aiming for much lower LDL levels than previously (1-1.5mmol/L compared with the previously suggested 3mmol/L). The levels now suggested are closer to that seen in wild animals and hunter-gatherer societies where atherosclerosis is rare (147).

4. Clotting-Bleeding Axis

There are not many single therapies that achieve more than a 30% response in event reduction. I believe the reason for this is related to inherent clotting-bleeding tendencies for each individual. Around one third of the population is prone to thrombosis, one third to bleeding and the final one third in the intermediate range depending on the clinical circumstances. At either end of this spectrum are the obvious clinical disorders which involve only a small minority of the population. On one hand, there are a small amount of haemophiliacs and sufferers of Von Willebrand's disease, as opposed to the larger amount of more non-specific bleeders with no detectable bleeding diathesis on laboratory testing. At the other end of the bell shaped curve is the small proportion of people with specific thrombotic disorders.

I do not believe, therefore, all people should be consuming prophylactic aspirin because of the 30% long-

term risk of bleeding in those predisposed.

All patients without an obvious bleeding diathesis or significant contraindication with either proven vascular disease or at very high risk (as determined by the full screening process) should be taking some form of blood thinning agent - either anti-platelet or anti-coagulant.

5. Treatment of Other Conditions

Strong risk factors such as hypertension, diabetes or other chronic diseases need appropriate, aggressive management. There is no point achieving target lipid values if the patient is left with poorly treated blood pressure, diabetes or a chronic inflammatory disorder.

SUMMARY

Atherosclerosis and its complications account for the greatest morbidity and mortality in the modern world. An accurate understanding of the incidence, pathogenesis, modes of presentation, investigation and management are vital for the development of appropriate and achievable preventative and monitoring strategies. Therefore, early screening along with risk factor analysis must be the cornerstone of a preventative screening program.

Arterial Stiffness is an established risk factor for the presence of atherosclerosis. Methods for measuring arterial stiffness are simple, quick and non-invasive in addition to being reproducible and inexpensive. Utilizing the strong relationship between arterial stiffness and cardiovascular risk factors to identify those at risk at an early stage may enable appropriate management of atherosclerosis.

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