“FOCUS ON” session:

Carotid stenosis. Epidemiology, natural history and clinical management
Cardiovascular risk assessment using ultrasound: the value of arterial wall changes including the presence, severity and character of plaques

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Abstract
Conventional cardiovascular risk factors have been used to identify subgroups at increased risk of cardiovascular events. The British Regional Heart Study Score (BRHSS) using such risk factors at best identifies only 59% of individuals that develop coronary heart disease (CHD) in the subsequent 5 years.

To identify a high risk subgroup in the BRHS a new approach has been the use of ultrasound to study arterial wall thickening, presence or absence of plaques and plaque type, to try and increase the predictive value of the BRHS Score.

Methods: Two towns (Dewsbury and Maidstone) of the British Regional Heart Study were selected because they have the highest and lowest prevalence of cardiovascular disease in the U.K respectively. A total of 418 men and 397 women were surveyed and their carotid and common femoral bifurcations scanned.

Results: Total plaque thickness, carotid intima-media thickness (IMT), ultrasonic arterial score (UAS) and sum of plaque types reversed, were found to be the most significant explanatory variables in a multiple linear regression model with an \( r = 0.505 \) and \( R^2 = 0.255 \). They could identify a subgroup of 25% of the population that contained 78% of cardiovascular deaths.

Conclusion: These findings appear to suggest the presence of plaques, the collective information from the echomorphology of these lesions and their absolute measures are far more predictive of risk.

At the beginning of the 20th century, cardiovascular disease (CVD) accounted for less than 10 percent of all deaths worldwide. At its end, CVD accounted for nearly half of all deaths in the developed world and 25 percent in the developing world (World Health Report, 1999; Yusuf et al, 2001). By 2020, CVD will claim 25 million deaths annually and coronary heart disease (CHD) will surpass infectious disease as the world’s number one cause of death and disability.

In an attempt to identify individuals at increased risk for premature MIs, strokes or death a number of studies have used well known conventional risk factors, such as age, smoking, raised cholesterol, or high blood pressure. These studies have followed up populations for many years and as a result have produced several risk assessment formulae or equations based on such risk factors.

The most widely used quantitative system of cardiovascular risk assessment has been the Framingham equation (Anderson et al 1990), which was developed for predicting risks of CHD, death from CHD, MI, stroke, cardiovascular disease and death from cardiovascular disease (Wilson et al, 1998). Other cardiovascular disease risk assessment tools have also been developed such as the PROCAM scoring system.
(Assmann et al, 2002), Sheffield table system (Haq et al, 1995) and the BRHS scoring system (Shaper et al, 1987).

Although these assessment equations can provide a logical approach to stratification of risk, none are perfect and a basic problem that exists for all these scoring systems is their predictive capacity. Although these systems identify high risk groups (with a 20-30% incidence of events), the majority of cardiovascular events occur among individuals who are not in this high risk category. For example, in the MRFFIT screeners, age 35-39 followed over 16 years, 56% of the MI’s occurred among men with baseline total cholesterol between 4.1 – 6.2 mmol/l and only 14% among those with cholesterols of greater than 7.3 mmol/l (Stampfer et al, 1999).

The relatively poor specificity of these equations may be because there are still many unknown risk factors. During the last 10 years emerging risk factors such as homocysteine, nutritional disturbances, or important protective or adverse genetic risk factors that are only now being identified, and so have never been used in prospective studies on risk. Whatever the reasons, these additional patients without obvious clinical risk factors but nevertheless at increased risk should be identified before the clinical events occur. Thus, to identify subjects in the population who have an increased risk of heart attack or stroke that cannot presently be predicted is a major challenge.

Controlling some of the risk factors associated with the development of atherosclerosis has been shown to reduce clinical events in patients with established clinical disease (The Scandinavian Simvastatin Survival Study Group, 1994; Rubins et al, 1999; Sacks et al, 2000). It has been suggested that a similar effect may be found in individuals with diseased vessels who have not yet developed evidence of symptomatic atherosclerosis. In order to study such vessel changes, before the development of symptoms, a noninvasive accurate method to quantify the arterial wall changes as a result of atherosclerosis is needed thereby identifying individuals at risk. These criteria appear to have been fulfilled with the use of high-resolution B-mode ultrasound.

In recent years, the possibility of measuring vessel wall abnormalities with ultrasound has gained increasing interest. Studies of intima-media thickness, as determined by ultrasound, have been validated on autopsy studies (Pignoli et al, 1986) and animal studies (Bond et al, 1986), and these show good correlation. Ultrasound measurement of the thickness of the wall of major arteries has been shown to be feasible and reproducible (Salonen et al 1991; Persson et al, 1992; Bots, 1993; Willekes et al, 1999; Griffin and Nicolaides, 2002). In particular ultrasound methods have become frequently used in studies on progression and regression of atherosclerosis. Early stages of the disease are studied by measuring intima-media thickness (IMT), mostly at different levels of the carotid artery (Crouse et al, 1986; Pignoli et al, 1986; Salonen R et al 1988; Wendelhag et al, 1992; O’Leary et al, 1999).

By looking at arteries with ultrasound, we can see the end result of all known and unknown, environmental and genetic risk factors. The thickness of the arterial intima and media and the size and nature (stable or unstable) of cholesterol deposits or plaques can be measured objectively and noninvasively using ultrasound. Our group and others have demonstrated that these measurements are good predictors of risk.

Several studies have demonstrated that increased intima-media thickness (IMT) of the carotid arterial wall measured with ultrasound is associated with an increased cardiovascular risk (Poli et al, 1988; Margitic et al, 1991; Salonen and Salonen, 1991; Markussis et al, 1992; Geroulakos et al, 1994).

Our group has recently shown that the main component of IMT responsible for the association with increased or decreased risk is the presence or absence of plaques (Ebrahim et al, 1999). Other natural history studies have shown the value of arterial wall measurements using ultrasound. The first was a prospective study of 2000 non-diabetic and non-hyperlipidemic individuals followed up for 6 years. It was found that the presence of plaque in the worst artery from four arteries (both common carotid and common femoral bifurcations) scanned proved to be a good predictor for risk. It was found that 59 of 217 individuals (27%) who had at least one artery with a plaque developed an event at 6 years, whereas cardiovascular events during the follow up period were rare if plaques or intima-media thickening was absent, occurring in 10 of 1783 individuals (0.56%). The 6-year event rate was 18.4% for small plaques compared to 42% for large plaques producing greater than 50% stenosis (Belcaro et al, 1996). These results were then confirmed in a second parallel study in which 10,000 individuals had been followed up for a minimum of 10 years (Belcaro et al, 2001).

In a third prospective study of 800 individuals who were part of the British Regional Heart Study (Ebrahim et al, 1999). Risk was assessed from the British Regional Heart Study Score (BRHSS). Both carotid and common femoral bifurcations were scanned with ultrasound. The total number of arteries with plaque (0-4) present, the sum of all plaque thicknesses (a measure of the severity of atherosclerosis) and the presence of echolucent plaques (echolucency is a measure of plaque instability) were found to be independent predictors of risk (Griffin and Nicolaides, 2002). These findings have now been validated on the basis of cardiovascular events at 6 years.

Ultrasonic measurements alone identified a high risk group of 25% of the population that contained 72% (p = 0.00001) of the cardiovascular deaths. Of the conventional risk factors, only age or the presence of diabetes was shown to improve the predictive model based on ultrasound. When age and diabetes were used in combination with the ultrasonic measurements, an even higher risk group could be identified consisting of 25% of the population that contained 78.6% (p = 0.00001) of the cardiovascular deaths (Griffin and Nicolaides, 2002).

It has now been demonstrated that aggressive risk factor modification is effective in preventing heart attacks and
strokes. The CARE and LIPID studies have shown that pro-
phylactic treatment with a lipid lowering agent taken orally
(pravastatin) produces an overall 35% reduction in heart
attacks and a 23% reduction of non-haemorrhagic strokes in
individuals with atherosclerosis (Lewis et al, 1998; The LIPID
Study Group, 1998; Byington et al, 2001). This effect is pres-
ent even in the older groups and in those who have a normal
cholesterol blood level, and is achieved by stabilizing athero-
sclerotic plaques (Crisby et al, 2001).

The results of the MRC/BHF Heart Protection Study of
cholesterol lowering with simvastatin in 20,536 high risk indi-
viduals (either because of an event or because of the presence
of peripheral arterial disease) but without a clear indication for
cholesterol lowering therapy have demonstrated a clear bene-
fit. This was particularly so in women, people older than 70
years, people with diabetes and those with normal or below
normal cholesterol (LDL<120 mg/dL). (MRC/BHF Heart
Protection Study Collaborative Group, 2002). Events such as
heart attacks, stroke and arterial surgery were reduced by one
third. Serious side effects were very rare. The observation that
benefits are independent of initial lipid values raises the possi-
bility of statin prescription without cholesterol monitoring.

Such advances in prevention research have spurred enthusi-
asm for primary prevention and risk assessment in asympto-
matic people. Lipid-lowering trials have demonstrated that pri-
mary prevention of coronary events is feasible, evidenced by
the West of Scotland Coronary Primary Prevention Study
(WOSCOPS) trial (Shepherd et al, 1995) of pravastatin in
hypercholesterolaemic men and by the Air Force/Texas
Coronary Atherosclerosis Prevention Study
(AFCAPS/TexCAPS) trial events (Downs et al, 1998) that
used lovastatin in average or typical risk men and women with
only moderate lipid abnormalities.

For clinicians, identifying a successful strategy to target
such individuals is of critical importance, but the greatest
importance is in trying to identify such persons in the first
instance. Arterial wall changes observed by ultrasound can be
a powerful epidemiological and risk predicting tool.
Ultrasound provides a noninvasive, practical and feasible
screening method. Not only can it define the high risk individ-
ual, who might otherwise be classed in a moderate - low risk
category from absence of clinical risk factors, but it also has
the potential to develop into a test that could reassure and con-
firm an individual’s low risk status. New guidelines on improv-
ing coronary heart disease assessment add support to the selec-
tive approach of such noninvasive testing (Smith et al, 2000;
Greenland et al, 2001; Kuller, 2001; Pearson 2002). The abili-
ty to assess and stratify risk early in an individual’s life could
allow implementation of the most effective strategy that in turn
may halt the scourge of the world’s number one killer.

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