

*Editorial***Use of B mode ultrasound of peripheral arteries as an end point in clinical trials**

The costs of large trials have led investigators to consider intermediate end points such as modification of risk factors or early manifestations of disease. For example, the degree of stenosis in coronary vessels has been measured directly by serial angiography.¹ B Mode ultrasound is a non-invasive method of examining the arterial wall for stenosis and plaques and for measuring the thickness of the intima-media complex. There is considerable interest in using these non-invasive measures as surrogate end points to evaluate new interventions. But are they any good?

Intima-media thickness

Lines defining the intima-media complex in an artery (figs 1 and 2) can be identified and the distance between them corresponds closely with the intima-media thickness measured histologically, with differences of only 4% and 9% in the carotid and femoral arteries respectively. In healthy adults the intima-media thickness (IMT) ranges from 0.25 mm to 1.5 mm (mean (SD) 0.77 (0.19) mm)² and values over 1.00 mm are often regarded as abnormal.³ Because the thickness of the intima-media complex is increased by smooth muscle hypertrophy and hyperplasia (key components of atherogenesis) IMT has

been used as a general measure of the severity of atheroma in symptom free people and as an intermediate (or the only) end point in clinical trials of new interventions.⁴

Reliability and validity of IMT measurement**RELIABILITY**

A difference of about 0.15 mm (for example, the difference between healthy and hypertensive subjects) can be clinically important; but such a difference can be produced by between or even within observer variation. The reliability of IMT measured by observers examining the same patients has 95% limits of agreement of ± 0.13 – 0.15 mm between observers and ± 0.06 – 0.13 mm within observers.^{2,5} Because measurement error is so large in relation to clinically important differences, any bias in measurement can lead to spurious findings. Measurement error between observers is greater than when the same observer looks at the same images. The implications are that if possible only one observer should be used, that observers must be blinded to the treatment received, and that it is essential to have standardisation of protocols and estimates of reliability in multicentre and long duration studies using several observers. Computer

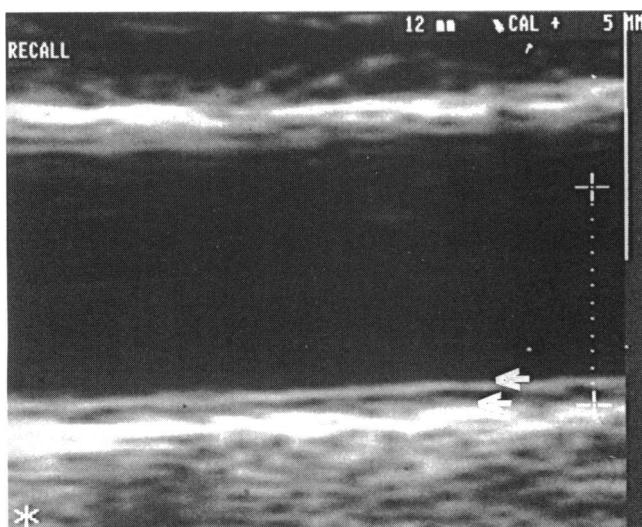


Figure 1 Longitudinal ultrasound image of the distal common carotid artery. Arrows mark the intima-media thickness of the posterior wall, which is normal.

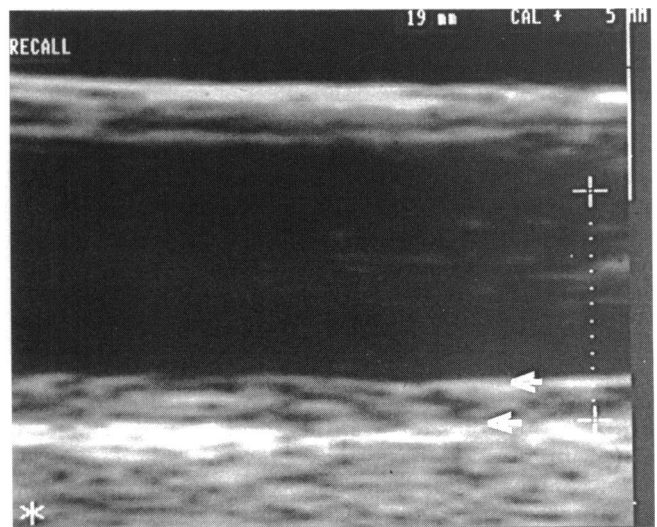


Figure 2 Longitudinal ultrasound image of the distal common carotid artery. Arrows mark the intima-media thickness of the posterior wall, which is thickened and abnormal.

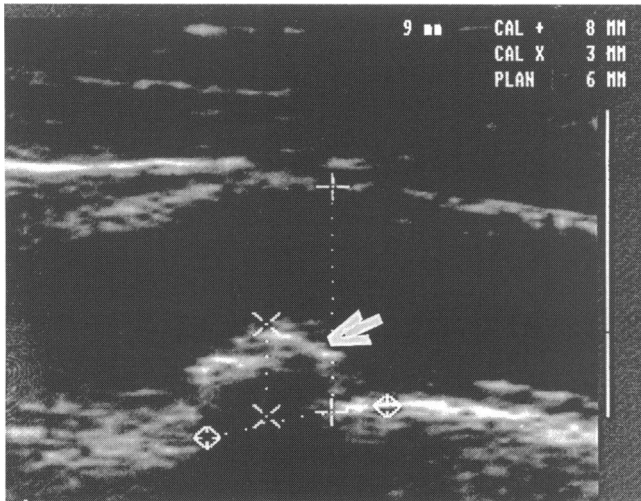


Figure 3 Longitudinal ultrasound image of the proximal common carotid artery. Arrow indicates a raised plaque in the lumen of the vessel.

algorithms are being developed to measure IMT automatically. This should considerably reduce measurement error and improve reliability.

VALIDITY

Validity has been assessed by comparing IMT in people with and without cardiovascular risk factors and cardiovascular disease. Clinical case series may give a false impression of validity because of selection bias caused by concurrence of symptoms and referral to a specialist centre. Cross sectional epidemiological studies have shown strong relations between smoking, hypertension, raised lipids, and IMT.²⁻⁸ A strong correlation between the British Regional Heart Study risk score, which predicts subsequent risk of myocardial infarction, and IMT in a clinical series of patients has recently been reported.⁹ The presence of cardiovascular disease or diabetes mellitus strengthens the relations between risk factors and IMT. Age is the most powerful determinant of IMT, which increases by about 0.01–0.02 mm a year,⁸ and comparisons must be age adjusted to make allowance for this.

In cross sectional studies IMT is associated with the presence of carotid artery stenosis, prevalent strokes, and transient ischaemic attacks. Allowance for age and other risk factors that are associated with both increased risk of disease and with increased IMT reduces the strength of association.^{2,6,10} These studies do not show whether increased IMT is of prognostic importance or is simply an epiphenomenon (that is, a physiological adaptation to increased blood pressure or an effect of aging).

Prospective epidemiological studies are necessary to assess the prognostic significance of variation in IMT. There has been only one. This reported findings in 1257 Finnish men who had 36 acute myocardial infarctions over 2 years.³ Any atherosclerotic lesion in the carotid artery (IMT thickening of ≥ 1.0 mm, plaques, or stenosis) increased the risk of acute myocardial infarction threefold (95% confidence interval 1.4 to 6.5). IMT thickening on its own, however, was not significantly associated with subsequent acute myocardial infarction (relative risk 2.1, 95% CI 0.8 to 5.2). Age adjustment further reduced the relative risk associated with IMT and also with plaques. Given the small number of events studied and the importance of control for confounding factors, it is uncertain whether IMT is independently associated with an increased risk of subsequent cardiovascular disease events. We need bigger studies of representative populations followed up for longer.

Natural history of IMT and plaques detected by ultrasound

Regression of lesions and reduction of IMT in patients on treatment would suggest that the measure may be of value as an end point in clinical trials. Regression of plaques detected by ultrasound is rare. IMT increases by about 0.5 mm a year in patients with diabetes, hyperlipidaemia, or hypertension who are being optimally treated.¹¹ Increases in IMT over 2 years in healthy Finnish men were just as large as increases in clinical series of patients, and the rate of increase was not correlated with established cardiovascular risk factors.³ These findings suggest that IMT may not be of use as a measure of early atherosclerosis or avoidable clinical disease.

Lipid lowering may be associated with the angiographic appearances of “regression” (that is, an increased lumen or reduction in arterial obstruction): these changes, however, may not be equivalent to histopathological regression of atheroma.¹ Complex interactions between arterial wall damage, the flow characteristics of vessels, and blood constituents determine the risk of clinical events. IMT gives an indication of only one aspect of the pathophysiological process and is not equivalent to angiographic “regression”.

Use of IMT as an end point in clinical trials

In conventional trials that use clinical events as end points thousands of patients must be studied to obtain adequate statistical power. The major advantage of using IMT is that every patient randomised produces an end point (provided that they survive) and adequate statistical power is achieved with much smaller sample sizes. This may be attractive in testing promising drugs before carrying out much larger studies that use disease events as end points.¹²

CURRENT EXPERIENCE

Several randomised controlled trials of lipid lowering drugs and antihypertensives are now underway with IMT as a major trial end point. The entry criteria for these trials include the presence of lesions detected by ultrasound that are potentially reversible (that is, plaques or an above average IMT or both), which halves the patients available for a trial.¹²

One study comparing colestipol and niacin with placebo has reported findings at 4 years⁴ among a subset of patients. In patients on treatment IMT got smaller during the first 2 years (-0.05 mm) and stabilised over the subsequent 2 years (although vessel lumens in the treated group got smaller) compared with a placebo group in whom IMT increased ($+0.04$ mm). The analysis of subsets may have led to poor comparability of placebo and treatment groups and further intention to treat analyses from this and other trials are awaited with interest.

TREATMENT EFFECTS

The pathophysiological meaning of IMT is not understood. Drugs may reduce cardiovascular disease risk by a wide range of mechanisms, some of which may be related to IMT (for example, reduced lipid deposition and smooth muscle hypertrophy) but many of which are not (for example, platelet disaggregation, stabilisation of plaques, increased blood flow). Widespread use of ultrasound measures as a major end point will lead to loss of potentially beneficial drugs that may reduce risk of clinical events but have no impact on IMT.

DEATH: A COMPETING END POINT

In trials of patients at high risk of cardiovascular disease

it is likely that some will die and will not have an IMT measurement. Death rates can be as high as 10% per year in high risk, older subjects and this level of loss could reduce the comparability of treatment and placebo groups and lead to bias in IMT end points.

GENERALISABILITY

The generalisability of trial findings from a carefully selected study group to the more typical patients seen in primary care and district hospitals is vital if a trial is to have clinical value and lead to changes in medical practice. The extremely large international studies of infarct survival (ISIS) after thrombolysis have had a major impact because they were generalisable to patients in many different clinical settings.

Conclusions

The current interest in using IMT as a trial end point for lipid lowering drugs and other treatments for atheroma is logical if it is assumed that changes in IMT correlate with the rate at which lipid-rich plaques are likely to progress to fissure and clinical events. The evidence to support such an assumption is not available. Very few plaques seem to be dangerous and likely to progress to clinical events. Consequently treatments that reduce plaque size, volume, or IMT may have very little effect on clinical events and vice versa.

Clinical decision making is based on efficacy, side effects and costs of treatment. How much should we be prepared to pay for a reduction of 0.05 mm in carotid IMT? The value of IMT end points is uncertain given current understanding of the meaning of the measurement. Large scale prospective epidemiological studies using ultrasound are required to examine the feasibility, utility, and importance of IMT. If epidemiological studies support the prognostic value of IMT, these end points will be of value in early, small scale trials of promising drugs that aim to reduce the rate of progression of

atheroma. Ultrasound measures may also be of value in assessing the severity of atheroma and in defining high risk groups for intervention. Larger trials using clinical end points will always be required to establish the clinical benefits, risks, and costs of treatments and thereby change clinical practice.

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The photographs of intima-media thickness and plaque were supplied by Professor A Nicolaidis, St Mary's Hospital Medical School, London.

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