Stroke and cholesterol: ‘Enigma Variations’?

ABSTRACT – The relationship of raised serum cholesterol to coronary atherosclerosis, the main pathophysiological substrate for most ischaemic myocardial events, is clear. Strokes have a more complex aetiology. Hypertension and smoking are strong risk factors for stroke, and their elimination is effective in stroke prevention, but cholesterol has been regarded historically as a poor predictor of stroke incidence. The reasons for this are analysed and the relevance of serum cholesterol to stroke prevention discussed.

In his original programme notes on the Enigma Variations, Elgar wrote ‘the principal Theme never appears’ and ‘the chief character is never on the stage’. As a stroke risk factor, serum cholesterol is similarly elusive and a poor predictor of stroke incidence, yet it is a major participant in atherosclerosis. Atherosclerosis in carotid, vertebral and basilar arteries, the basal cerebral arteries of the Circle of Willis, as well as elsewhere, and ‘microatheroma’ affecting small deep penetrating branches of the middle and posterior cerebral arteries are to a varying extent possible precursors of thromboembolic or thrombo-occlusive stroke. If cholesterol is the ‘enigma’, the ‘variations’ might be construed as reasons why serum cholesterol fails to emerge as a consistent stroke risk factor.

Risk factor interactions

Cholesterol may remain concealed because of difficulties in interpreting logistic regression coefficients in prospective observational studies. If two risk factors are correlated, measuring the effect of one on a disease while controlling for the other inevitably controls part of the variability of the risk factor under investigation. A significant univariate predictor of disease may thus fail to be a significant independent predictor on multivariate analysis, or its significance become attenuated, if most or some of its effect is manifest through the relationship of a covariate with the disease. Risk factors affecting atherosclerosis are likely to be interrelated in complex ways. For example, hypertension increases atherosclerosis, as do diabetes mellitus, hypertriglyceridaemia, raised lipoprotein (a), fibrinogen and smoking. When these are viewed as potentially confounding variables in assessing the risk factor status of cholesterol, the significance of the latter might be reduced or lost. Statistical techniques such as projected slope analysis can address this difficulty.

On the assumption that serum cholesterol acts through the pathological substrate of atherosclerosis, a more fundamental problem with it as a risk factor is its dependence on age for clinical expression. Atherosclerosis is a gradual and steady progressive process from childhood to old age, reaching a clinical threshold only when plaques eventually become unstable and subject to the sudden complications of fissuring, rupture, haemorrhage, thrombosis or embolism. Clarification of the relationship between cholesterol as a risk factor and age is therefore central to an understanding of how serum cholesterol level may influence stroke incidence even when univariate or multivariate analysis fails to demonstrate an association.

Clinical outcomes of atherosclerosis

Another reason proposed for cholesterol’s poor risk factor credentials has been the temporal pattern of development of atherosclerosis, tending initially to be aortic, then coronary and finally increasingly cerebrovascular and peripheral. This temporal sequencing of coronary heart disease (CHD) and stroke has been put forward as an explanation for the reduced statistical association of serum cholesterol with stroke, in that many who might otherwise suffer stroke succumb instead through competing risk to CHD, which either proves fatal or may result in radical risk factor intervention.

This is well illustrated by a study of cholesterol as a risk factor for CHD and stroke in Hawaiian Japanese men. A fortuitous overall lower CHD rate in this cohort than among US white men, together with an overall stroke rate approximating that for US white men and a 15-year follow-up, enabled a positive association to emerge between cholesterol level and stroke. This is in sharp contrast to other prospective observational studies dominated by CHD which demonstrated no such relationship. Interestingly, in the Hawaiian Japanese subjects a relative risk of 1.6 for CHD in men under 60 was the same as for thromboembolic stroke in men over 60. On the other hand, no association of total cholesterol with stroke was found in a large but disparate prospective database, whether or not those with existing CHD were excluded.

Cholesterol subfractions

The different effects of cholesterol subfractions, particularly high-density lipoprotein (HDL) cholesterol acting protectively, may mask a real association between low-density lipoprotein (LDL) cholesterol and stroke if only total serum cholesterol is measured. For this reason, total serum cholesterol is likely to be at best only a crude indicator of atherosclerosis, for
example in those taking moderate alcohol and in premenopausal women, where inconsistencies are introduced by a greater proportion of the total serum cholesterol representing protection rather than risk. If total serum cholesterol has its problems as a reliable risk factor, perhaps caution should also be exercised against placing too much emphasis on the cholesterol moiety of LDL. Uptake of oxidised LDL by macrophages is but one facet of the complex process of atherogenesis, which additionally involves endothelial dysfunction, an array of cytokines, inflammation, expression of HLA class II molecules, smooth muscle proliferation and migration, angiogenesis (one cause of destabilisation of advanced plaques through haemorrhage into them), and fibrosis – even chlamydiae have been found in atherosclerotic plaques. Nevertheless, because LDL remains a critical component, if no longer ‘a sufficient cause’ of atherosclerosis, bound cholesterol will at least continue to be regarded as a useful marker of disease activity.

**Stroke subtypes**

A correct classification of stroke subtypes is of considerable importance for the proper appraisal of cholesterol as a stroke risk factor. Atherosclerosis may be responsible for far fewer strokes than previously realised, and indeed for a minority of all strokes. The lack of association of lacunar stroke with serum cholesterol (because of a different postulated aetiology in most, but not all, cases) and a possible, though disputed, negative association with haemorrhagic stroke, may negate a true association between cholesterol and stroke in macrovascular disease. Strokes thought to originate from atrial fibrillation – and indeed any stroke not putatively linked to atherogenesis – must also be excluded from the reckoning.

These points are exemplified in a recent paper appropriately entitled ‘Lipids and stroke: a paradox resolved’. Presumed atherothrombotic strokes confirmed by diagnostic arterial imaging were selected (90 consecutive patients) together with a carefully age- and community-matched control group. Hypertension, CHD and smoking in the two groups were taken into account by multivariate analysis. The results showed that total serum cholesterol, LDL cholesterol and serum triglyceride were all significantly higher in the stroke group, whereas HDL cholesterol was significantly lower, independent of the other risk factors.

A pathological correlate for this study is provided by an investigation of lipid profiles and the prevalence of carotid atherosclerosis in a population in Eastern Finland, an area with an exceptionally high incidence of CHD and therefore, like Scotland, a rich ‘hunting ground’ for seekers of generalised atherosclerosis. Carotid ultrasonography of men from this population revealed that the presence of carotid atherosclerosis increased steadily with age, from 14.1% at 42 years to 81.9% at 60 years. The mean adjusted LDL cholesterol was 3.67 mmol/l for subjects free of carotid atherosclerosis and 4.02 mmol/l in those with atherosclerotic changes (at least intimal thickening). Furthermore, serum LDL cholesterol and HDL cholesterol (inverse) remained significant in a multivariate regression model adjusted for age, obesity, plasma fibrinogen, cigarette years and duration of hypertension.

Correlations between cholesterol, carotid atherosclerosis (an example of macrovascular disease) and cortical infarction are now reasonably well established, but the situation with respect to cholesterol, microvascular intracerebral disease and lacunar strokes remains far from clear. The main reason is that lacunar strokes have turned out to be a heterogeneous group with various aetiologies that defy accurate clinical and investigational determination. Historically, lacunar strokes were thought to reflect ‘arteriosclerotic’ (or at least non-atherosclerotic) damage to small penetrating arteries, with hypertension the main risk factor and either lacunar infarction or intracerebral haemorrhage the main clinical manifestations on the basis of fibrinoid necrosis resulting in vessel occlusion or rupture, or rupture of microaneurysms. In this view, there is no relationship between lacunar infarction and atherosclerosis or dyslipidaemia – and low serum cholesterol is characteristic (even interpreted by some as indicating that low cholesterol is a positive risk factor for lacunar stroke). On the other hand, there has been growing evidence over recent years that another group of lacunar infarctions may be associated with atheroma located, for example, in the middle cerebral artery or in penetrating arteries usually near their origins. Yet other lacunar infarctions are undoubtedly produced by small emboli arising from neck arteries or even the fibrillating heart, though both small and larger emboli are statistically much more likely to impact in the distribution of the main intracerebral arteries, causing cortical infarction.

Clinical lacunar syndromes cannot distinguish reliably between all these different aetiologies, as perhaps emphasised by their correlation with accepted risk factors for either microvascular or macrovascular disease, or both (hypertension, diabetes, CHD). Cerebral imaging provides some clues, in that subjects with microvascular disease are more likely to demonstrate multiple asymptomatic lacunes, hypertension and periventricular white matter hypodensities (leukoaraiosis) on computed tomography. An association of multiple asymptomatic lacunes with arteriosclerosis, particularly affecting long medullary arteries in the frontal lobes (as well as deep penetrating arteries), was confirmed in an autopsy study that noted a higher prevalence with hypertension and advancing age. This study also suggested ‘autoregulatory failure of cerebral blood flow’ as a possible mechanism for lacunes, especially perhaps in neuropsychiatric degenerative disease. In some populations with a high risk of
stroke (whether infarction or haemorrhage), but with a ‘paradoxically’ low risk of CHD, autopsy examination has shown that the excess stroke risk depends not on atherosclerosis in cerebral arteries but on small vessel arteriosclerosis. When CHD occurs in such populations, it correlates well with atherosclerosis in the cerebrovascular tree, but stroke in the absence of CHD is characteristically associated with low serum cholesterol, high alcohol and perhaps some aspect of diet such as low intake of food from animal sources21,22.

Autopsy studies of cases across the range of micro and macrovascular disease are most likely to reveal a diverse aetiology for lacunar stroke. The Akita pathology study23, which specifically compared serum cholesterol levels in Japanese men with cerebral arterial narrowing at subsequent autopsy, found that cortical infarction was related both to the highest serum cholesterol levels and to the most extensive atherosclerosis (and stenosis) in the basal cerebral arteries (0.2-6 mm diameter) but not to stenosis in penetrating arteries (100-300 μm diameter). Cerebral haemorrhage correlated well with low mean serum cholesterol and with either low stenoses rates in both basal and penetrating arteries or significant stenosis in penetrating arteries only, and was ascribed to rupture of penetrating artery microaneurysms caused by angioneurosis (fibrinoid necrosis). Unlike atherosclerosis, this process involved no lipid deposition in the intima, but there was loss of medial smooth muscle cells, infiltration of plasma into the intima, histolysis of internal elastic lamina and intimal collagen fibres, intimal fibrin deposition and luminal dilatation. Cholesterol was not so low in cases of cerebral haemorrhage if stenoses were found in either basal or penetrating arteries. Cases of penetrating artery infarction tended to have intermediate elevations of serum cholesterol and to be associated with stenosis of both basal and penetrating arteries. These were assumed to be complications of arteriosclerosis. Significantly, though, only one histopathological microscopic slide at the level of the basal ganglia was used to assess penetrating artery stenosis, so areas of isolated stenosis of small arteries as might be caused by localised atheroma, although rarely seen, may have been underestimated23.

Cholesterol – a significant concealed risk factor: age – a spurious risk factor?

This section explores the relationship between LDL cholesterol, atherosclerosis, age and those cerebrovascular events that have their origin in arteriosclerosis. As knowledge advances, all disease risks currently ascribed to age will necessarily be explained by other more tangible variables. Statements such as ‘ageing, diabetes, smoking, hypertension, and obesity have all been implicated in the pathogenesis of stroke’ are therefore potentially misleading24. Taking the Medical Research Council’s mild hypertension trial as an example25, the relative risk for stroke in men in the untreated group was found by multiple logistic regression analysis to be 1.53 for a five-year increase in age whereas it was only 1.05 for a 1 mmol/l difference in cholesterol over roughly the same period. Corresponding figures were 1.99 per 20 cigarettes smoked daily, 1.34 for a 10 mmHg increase in systolic blood pressure and 1.39 for an ischaemic ECG. Concealed in the considerable age-related risk must be risks that should rightly be ascribed elsewhere. This is more likely in respect of risk factors that act very slowly over a long period of time before reaching a threshold of clinical expression, one of which may be the putative stroke risk factor LDL cholesterol. By contrast, the accepted risk factors of hypertension and smoking have significant effects on stroke incidence within the relatively short span of clinical studies, an indication perhaps that some, or most, of their effects may not be mediated through atherosclerosis. This could be one reason, for example, why treating hypertension has a more rapid and profound effect on preventing stroke than on preventing myocardial infarction26.

If serum LDL cholesterol concentration remains relatively constant in an individual, or increases only slightly with age27, and bears a constant relationship to the evolution of atherosclerosis (itself assumed to increase linearly with age), a simple pathophysiological model may be generated to relate LDL cholesterol to the atherosclerotic stroke threshold. Clinical observational studies suggest that the slope of the ‘atherosclerosis against age’ graph varies markedly between individuals, with considerable dispersion along the threshold around the mean age of clinical expression for a given concentration of LDL cholesterol. This dispersion depends on a multiplicity of factors (some unknown) that affect the rate of atherogenesis, such as gender and genetic variations, and the interaction of diverse risk factors such as triglyceride, fibrinogen and other lipoprotein subfractions – and indeed most of the ‘variations’ already discussed. The situation is made more complicated because even small differences in slope between individuals will be magnified over the course of decades, increasing the dispersion for a given concentration of LDL cholesterol.

If coronary arteries are assumed in the model to be more susceptible to atherosclerosis, with a lower threshold of clinical expression than, for example, carotid arteries, the age of clinical presentation will be younger, and the frequency of clinical events higher, for the coronary rather than for the carotid circulation. It is also likely that dispersion along the threshold of clinical expression in the ‘age against atherosclerosis’ graph for a given concentration of LDL cholesterol will be less for coronary than for carotid arteries. Therefore, at least part of the relationship between LDL cholesterol concentration and myocardial infarction might be demonstrable in observational studies, allowing LDL cholesterol to masquerade as a conventional...
risk factor. In the case of stroke, it is conceivable from the model that the weaker pathophysiological relationship between LDL cholesterol and atherosclerotic stroke might fail to be exposed altogether in non-interventional observational studies, giving the impression that LDL cholesterol is not a risk factor for atherosclerotic stroke, yet drug-induced reductions of LDL cholesterol might indicate a highly significant relationship between the two.

The model, which will be developed in a more rigorous way elsewhere, might also explain why a high level of LDL cholesterol in inherited hypercholesterolaemia predisposes to early stroke, and conversely, why low cholesterol at a young age appears less likely to be associated with stroke. In the younger age group there is less overlap of LDL cholesterol concentrations along the threshold of clinical expression but with increasing age, most concentrations across the normal LDL cholesterol range can, however, correspond with degrees of atherosclerosis capable of manifesting as strokes with approximately equal frequency. The main clinical opportunity stemming from the model is undoubtedly the prediction that any therapeutic intervention that reduces cholesterol effectively should reduce the rate of atherogenesis and lessen the chance of the stroke threshold being reached, particularly if cholesterol concentration can be reduced so much that a negative association of atherosclerosis with age can be achieved (regression of atherosclerosis). The level of cholesterol corresponding to zero slope in the ‘atherosclerosis against age’ graph (or a slope so shallow as not to reach the clinical threshold within a lifetime) is variable between individuals and unknown, but may be much lower than previously envisaged.

There are two interesting corollaries to this line of reasoning: first, if there is an atherosclerosis-related cerebral vascular event, the atherosclerotic clinical threshold must have been reached de facto, so vigorous cholesterol-lowering measures might be indicated whatever the level of serum cholesterol. Secondly, the prevention of stroke should be more effective when the atherogenic ‘marker’ of CHD, rather than transient ischaemic attack (TIA) or stroke itself, is used to initiate cholesterol-lowering treatment before the atherosclerotic threshold for stroke has been reached. The forthcoming Heart Protection Study should provide an ideal test-bed for this proposition, provided that the investigation and diagnosis of stroke is as rigorous as that of the coronary artery disease end-points.

**Cholesterol reduction**

If the importance of cholesterol as a stroke risk factor might truly be revealed only through large downward drug-induced reductions of cholesterol, this approach has already proved effective in recent primary and secondary CHD prevention trials using statins. There is at least circumstantial evidence from these trials of an effect of lipid lowering on stroke incidence. Pooled data from four pravastatin atherosclerosis regression trials (coronary or carotid) indicated a reduction in stroke incidence of 62% (p = 0.054) and the 4S simvastatin secondary prevention CHD trial reported a 30% reduction in fatal and non-fatal cerebral vascular events (p = 0.024), though these analyses were post hoc, the absolute numbers of stroke victims were small, and the reported diagnostic details sketchy. A 31% (p = 0.03) reduction in the frequency of stroke was briefly reported in the recent Cholesterol and Recurrent Events (CARE) study, a CHD secondary prevention trial in which pravastatin was used to lower cholesterol from baseline values in the range 5.50–8.00 mmol/l. A large, long-term pravastatin intervention study in Australia and New Zealand is expected to furnish similar results soon.

**Stroke prevention trials**

In 1996, there was still much uncertainty about the best strategy for stroke prevention. A meta-analysis of 10 randomised trials of the effectiveness of aspirin after TIA or non-disabling stroke suggested that any dose over 30 mg is likely to prevent only 13% of vascular events. Aspirin and dipyridamole may be equally protective but with additive benefits if co-prescribed (European Stroke Prevention Study 2). Warfarin is still being evaluated. The value of carotid endarterectomy after TIA has been established for stenoses of approximately 70–99%, but the benefits for milder degrees of stenosis have not been proven. As for primary prevention in 1996:

the management of individuals with severe asymptomatic carotid stenosis is based unfortunately on empirical guidelines and pragmatic decisions.

From the current perspective, clinical trials most likely to establish cholesterol-lowering as a means of secondary stroke prevention are those recruiting (male) subjects after suffering a TIA or a non-disabling stroke in the carotid territory in association with ipsilateral carotid disease. Regardless of the level of baseline cholesterol, treatment with a statin should aim at a cholesterol (or LDL) reduction of 20–40%, or perhaps a target level of LDL cholesterol level around 3.2 mmol/l, maintained over several years at least, and probably indefinitely. Because of the interaction of cholesterol with other risk factors, in particular hypertension, smoking and raised triglycerides, these should be assiduously controlled; for triglycerides, the inclusion of fibrates in the cholesterol-lowering regime might be appropriate. The predicted effect of treating cholesterol in conjunction with these other risk factors would be more than additive, and the resultant decrease in stroke incidence might even be dramatic in this high risk group. The benefits of cholesterol lowering, whether in a secondary or primary prevention setting, would be most apparent when established...
treatment is continued into old age where the absolute stroke incidence is highest.

Conclusion
A simple conclusion may be drawn: that cholesterol is implicated in any stroke whose origin is in atheroma, wherever this is located in the vascular tree and whatever the clinical manifestations; conversely, that cholesterol is not implicated in any stroke whose origin is in arteriosclerosis or any other pathologies, whatever the clinical manifestations, unless low cholesterol is accepted as a positive contributor to microvascular disease.

It will be for advances in technology to determine which clinical outcomes are associated with which pathologies because there is undoubtedly much uncertainty in this difficult area. From the arguments presented, it is inherently unlikely that meta-analysis of existing, often poorly focused, prospective observational studies will resolve the issue. On the other hand, properly designed controlled trials should determine unambiguously whether the incidence of truly atherosclerotic stroke is reduced by lowering serum LDL cholesterol. Pathophysiologically-based, computer-generated models may have a role in further elucidating complex risk factor interactions; risk currently attributed to age should gradually be whittled away and ascribed elsewhere. Hopefully, the ‘enigma’ of cholesterol will prove to be less durable than Elgar’s, and cholesterol will soon take its place centre stage (but with a carefully delineated role!) as a bona fide risk factor for atherosclerotic stroke and a key target for stroke prevention strategies.

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