Role of Lipids in the Development of Brain Infarction: The Framingham Study

BY WILLIAM B. KANNEL, M.D.,* TAVIA GORDON,* AND THOMAS R. DAWBER, M.D.t

Abstract:

An association of blood lipids with the development of atherothrombotic brain infarction under age 60 is demonstrated. This is based on 18 years' surveillance of 5,209 men and women, of whom 52 men and 59 women developed brain infarction. The relationship under age 60 was statistically significant only for men.

Triglyceride-rich pre-beta and cholesterol-rich beta lipoprotein were both related to the incidence of premature brain infarctions. Regardless of associated lipoprotein pattern, risk was proportional to serum cholesterol value, under age 60. On the other hand, pre-beta lipoprotein was unrelated to risk when associated cholesterol was taken into account.

At any lipid value risk of brain infarction varied greatly depending on the number and intensity of other contributors. Blood lipids are best considered as an ingredient of a stroke profile, and in the absence of other contributors to risk the influence of lipid is feeble.

Methods

At Framingham, men and women who were initially free of ABI have been followed for 18 years. In those persons free of stroke the relation of personal attributes to the subsequent development of ABI is being assessed. Early in the study each person was classified on the basis of their serum cholesterol, phospholipid, pre-beta and beta lipoprotein values as well as other risk factors believed to contribute to ABI. Laboratory methods employed, diagnostic criteria, sampling procedure, response rates and completeness of follow-up have been reported previously.8-11 The cholesterol determinations were made on each examination in the Framingham Study laboratory using the Abell method.12 Phospholipid was measured on each examination except for the fifth and sixth. Lipoprotein fractions were quantitatively measured under the supervision of Gofman using ultracentrifugal methods pioneered by his group.13 Cerebrovascular disease events have been ascertained over the ensuing 18 years by means of biennial examinations in the study clinic, daily surveillance of hospital admissions, and from death certificates. In addition, in recent years suspect cases admitted to the only hospital in town were evaluated in the hospital and on subsequent clinic visits to clarify diagnoses. In this way comprehensive surveillance of cerebrovascular morbidity and mortality has been achieved. Follow-up of the original cohort of 5,209 persons has been
satisfactory, with nearly 85% of the subjects taking every possible examination. Most of the rest have been examined at less frequent intervals. Internal evidence has revealed no indication that loss to examination has led to any substantial loss of information concerning the appearance of new stroke events.

Criteria for cerebrovascular disease have been uniformly applied. Detailed criteria have been reported elsewhere. Briefly, a diagnosis of ABI was made when a focal neurological deficit abruptly developed (e.g., hemiparesis, aphasia, homonymous hemianopia, hemihypesthesia) consistent with a vascular occlusion in the absence of a source for embolus, a bloody spinal fluid or other possible explanation.

The incidence of new ABI events evolving in the previously classified population cohort placed into subgroups according to their lipid values was determined. To adjust for any stratification by age resulting from classification into lipid subgroups, risk was expressed as a "morbidity ratio." This is the ratio of observed to expected cases of ABI multiplied by 100 to obtain whole numbers. The expected number of cases was determined by applying the age-specific ABI disease rates for the whole population cohort to the age composition of the lipid subgroups under consideration. Average annual incidence of ABI was computed according to person-years exposure to risk at a given cholesterol value at each biennial examination. The net and joint effect of lipids taking other risk factors into account was assessed by comparing univariate versus multivariate logistic regression coefficients according to the method of Walker and Duncan and Truett and Cornfield.

Two cautions should be observed in examining the data: (1) where persons are recharacterized on each examination this information is used for reclassifying persons, and age at event is as of the biennial examination preceding the event. (2) Where persons are characterized only at examination two, age is at that examination, while age at the event may be considerably older. Thus, the age distribution of cases may be quite different in these two types of tables — for example, tables 1 and 2.

The other caution is that the results of multivariate analysis may be very sensitive to the variables used, particularly when they are highly correlated. Thus, in table two the absolute differences are not as important as the relative changes...
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TABLE 2
Logistic Regression of 16-Year Incidence of ABI on Various Lipids at Examination Two, by Age and Sex: Framingham Study, 18-Year Follow-Up

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Serum cholesterol</th>
<th>Serum phospholipid</th>
<th>SF 0-20</th>
<th>SF 20-400</th>
<th>Serum cholesterol</th>
<th>Serum phospholipid</th>
<th>SF 0-20</th>
<th>SF 20-400</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;45</td>
<td>45-54</td>
<td>55-64</td>
<td>Average</td>
<td>&lt;45</td>
<td>45-54</td>
<td>55-64</td>
<td>Average</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>-1.242†</td>
<td>-0.059</td>
<td>0.289</td>
<td>0.423†</td>
<td>0.200</td>
<td>0.162</td>
<td>0.068</td>
<td>0.074</td>
</tr>
<tr>
<td>Serum phospholipid</td>
<td>1.542†</td>
<td>0.014</td>
<td>0.289</td>
<td>0.522†</td>
<td>-0.092</td>
<td>-0.204</td>
<td>0.010</td>
<td>-0.077</td>
</tr>
<tr>
<td>SF 0-20</td>
<td>0.485‡</td>
<td>-0.061</td>
<td>0.288</td>
<td>0.288</td>
<td>0.036</td>
<td>0.140</td>
<td>0.220</td>
<td>0.173</td>
</tr>
<tr>
<td>SF 20-400</td>
<td>0.848†</td>
<td>0.173</td>
<td>0.227</td>
<td>0.369†</td>
<td>-0.140</td>
<td>-0.140</td>
<td>0.144</td>
<td>0.068</td>
</tr>
</tbody>
</table>

*Estimates of coefficients by the method of Truett and Cornfield: \[ \hat{\beta} = \frac{\sum \beta_i V_i}{\sum \frac{1}{V_i}} \] where \( \beta_i \) is the age-specific coefficient and \( V_i \) is its variance.

†Significant at a level of 0.01 (T > 2.32).
‡Significant at a level of 0.05 (T > 1.64).

Results

Over 18 years of continuous follow-up 52 men and 59 women aged 30 to 62 years at entry developed clinical manifestations, which on review by a panel of investigators met criteria for ABI. The incidence rose with age in each sex with a male predominance only under age 55 (fig. 2).

Aside from age, serum cholesterol, blood pressure, and possibly carbohydrate tolerance appear to be the major biological determinants of the rate of atherogenesis in the heart, head and legs. At any age, risk of ABI is proportional to the degree of elevation of the blood pressure. ABI occurs in excess in diabetics whether otherwise at high or low risk. A substantial association of serum cholesterol with the development of ABI, however, can be demonstrated only in those under age 55, and a significant one only for men (fig. 3, table 1).

There is a high correlation among these lipids four lipids are included in the multivariate analysis, whereas in figure 1 only two lipids are included. Again, the results differ.
EIGHT YEAR PROBABILITY OF ATHEROTHROMBOTIC BRAIN INFARCTION ACCORDING TO SERUM CHOLESTEROL AND OTHER RISK FACTORS: MEN AGE 50: FRAMINGHAM STUDY: 18 YEAR FOLLOW-UP

**LOW RISK**
- No ECG-LVH, SBP=105,
- Non Smoker, No Glucose Intolerance

**HIGH RISK**
- ECG-LVH Present, SBP=195,
- Smoker, Glucose Intolerance Present

![Probability Chart](chart.png)

**SOURCE:** Framingham Monograph ^28

**FIGURE 3**

(table 3). One would anticipate, therefore, that all the measured lipids would tend to bear the same general relationship to the subsequent appearance of ABI, and this is, in fact, what the data show. For men under age 45 at examination two, all lipids measured on that examination are related to subsequent ABI incidence, with cholesterol and phospholipid seeming to have a stronger relationship to incidence than the beta and pre-beta lipoproteins (table 2). When the lipid measurements made at the second examination are entered simultaneously into a discriminant function, phospholipid emerges as the dominant variable. However, since phospholipid and cholesterol (unlike the lipoproteins) were remeasured on successive examinations, it is possible to take all this information into account by reclassifying people at each examination. When this is done for young men, either lipid by itself is predictive, but when they are considered jointly by multivariate analysis, cholesterol appears to be dominant over phospholipid in predicting ABI (table 4). Since the number of cases in this age-sex group is small a considerable variation is possible by chance alone; so that the most reasonable conclusion to draw is that either serum cholesterol or phospholipid may be used to assess the risk of a young man developing ABI but that it is not necessary to measure more than one of these lipids for the purposes of predicting this disease.

The S20-400 lipoprotein function is of particular interest since, in the fasting state, it is the major carrier of serum triglyceride and in a casual measure-

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**TABLE 3**

**Correlation Between Various Lipids: Framingham Study, Examination Two**

<table>
<thead>
<tr>
<th>Lipid</th>
<th>SF 0-20</th>
<th>SF 20-400</th>
<th>Phospholipid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol</td>
<td>0.67</td>
<td>0.43</td>
<td>0.63</td>
</tr>
<tr>
<td>SF 0-20</td>
<td></td>
<td>0.13</td>
<td>0.33</td>
</tr>
<tr>
<td>SF 20-400</td>
<td></td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>0.36</td>
<td>0.35</td>
<td>0.48</td>
</tr>
</tbody>
</table>

**Note:** Restricted to persons having all four measures available on the same examination. While the bulk of the determinations are from examination two, where this was missing, determinations were obtained (if available) from examination three or one.

Product moment correlations were computed for each ten-year age group and then averaged.
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TABLE 4
Logistic Regression of Two-Year Incidence of ABI on Serum Cholesterol and Phospholipid Levels by Age and Sex: Framingham Study, 18-Year Follow-Up

<table>
<thead>
<tr>
<th>Age at examination preceding event, sex</th>
<th>Univariate</th>
<th>Standardised coefficients</th>
<th>Rivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum cholesterol</td>
<td>Phospholipid</td>
<td>Serum cholesterol</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>1.353*</td>
<td>0.431</td>
<td>1.626*</td>
</tr>
<tr>
<td>55-64</td>
<td>0.011</td>
<td>0.262</td>
<td>-0.213</td>
</tr>
<tr>
<td>65-74</td>
<td>0.208</td>
<td>0.310</td>
<td>-0.047</td>
</tr>
<tr>
<td>Average†</td>
<td>0.325</td>
<td>0.309</td>
<td>0.219</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>-0.140</td>
<td>-0.823</td>
<td>0.480</td>
</tr>
<tr>
<td>55-64</td>
<td>-0.135</td>
<td>-0.203</td>
<td>-0.033</td>
</tr>
<tr>
<td>65-74</td>
<td>0.017</td>
<td>-0.194</td>
<td>0.404</td>
</tr>
<tr>
<td>Average†</td>
<td>-0.064</td>
<td>-0.291</td>
<td>0.209</td>
</tr>
</tbody>
</table>

*Significant at a level of 0.01 (T > 2.32).
†Regression coefficients computed by the method of Truett and Cornfield15: \( \beta_i \sum V_i / \sum 1 / V_i \), where \( \beta_i \) is the age-specific coefficient and \( V_i \) is its variance.

The relationship of this lipid to the incidence of ABI is statistically significant only for young men, although the average of the specific univariate regression coefficients for age groups 30 to 49, 50 to 54 and 55 to 64 (at examination two) is also statistically significant. Age-specific multivariate logistic regressions were also computed which included the variables systolic blood pressure, relative weight, blood glucose, uric acid and cigarette smoking as well as both serum cholesterol and S20-400. The average of these is represented in figure 1 on a standardized scale. The comparable graph for the age group 30 to 49 would look very similar. Clearly, if one’s sole interest is in assessing the risk of developing ABI there is little point in measuring S20-400 (and, by inference, triglyceride) when a serum cholesterol determination is available.

While both cholesterol and blood pressure contribute to risk of ABI, hypertension is by far the more powerful factor. This can be judged quantitatively from a comparison of the size of their respective regression coefficients suitably standardized for the different units of measurement involved (table 5).

From the foregoing it would appear that blood lipids are best conceptualized as an ingredient (a minor one at that) of a stroke profile. At any cholesterol value risk varies over an extremely wide range depending on the coexisting blood pressure and other factors (fig. 3). In the absence of other contributors to risk the influence of cholesterol (or any other lipid) is feeble indeed. Using a multiple logistic formulation18 it is possible to compute a handbook for the estimation of risk using a constellation of risk factors including cholesterol. Examination of a table from such a handbook places cholesterol in perspective and allows a synthesis of the joint effect of combinations of factors contributing to stroke on the probability of developing an ABI.19

Phospholipid has been considered to play, if anything, a protective role in atherogenesis as a sort of biological detergent to stabilize the other lipids in the watery blood. The evidence does not support that view. Risk of ABI in men under 55 is also directly proportional to the phospholipid concentration.11

**Discussion**

The data presented suggest a minor role of lipid in the development of ABI. The effect of lipid is vastly overshadowed by the impact of the coexisting blood

**TABLE 5**
Logistic Regression of Two-Year Incidence of ABI on Various Characteristics. Framingham Study: 18-Year Follow-Up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Average standardized regression coefficient Men</th>
<th>Average standardized regression coefficient Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>0.694</td>
<td>0.688</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>0.274</td>
<td>0.127*</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>0.267</td>
<td>-0.057*</td>
</tr>
<tr>
<td>Blood sugar</td>
<td>0.200</td>
<td>0.223</td>
</tr>
<tr>
<td>Relative weight</td>
<td>0.162*</td>
<td>0.436</td>
</tr>
<tr>
<td>Vital capacity/height</td>
<td>-0.258*</td>
<td>-0.215*</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>0.308</td>
<td>-0.016*</td>
</tr>
<tr>
<td>Cardiac enlargement (x-ray)</td>
<td>0.242</td>
<td>0.555</td>
</tr>
<tr>
<td>ECG-LVH</td>
<td>0.513</td>
<td>0.480</td>
</tr>
<tr>
<td>Non-specific ECG abnormality</td>
<td>0.270</td>
<td>0.317</td>
</tr>
</tbody>
</table>

*Coefficient not statistically significant at a 0.05 level (source: reference 11).
pressure. Evidently hypertension directly precipitates strokes as well as acting to promote accelerated atherogenesis. With ABIs occurring late in life, after exposure for several decades to the generally high lipid values in the U.S.A., most hypertensives appear to have enough lipid to produce cerebral atherosclerosis. More information is needed to assess the net effect of each major lipid in the development of cerebral atherosclerosis taking into account the joint effect of other lipids and other relevant factors which contribute to ABI incidence. The role of lipoprotein "types" according to current criteria remains to be assessed prospectively. However, the lipoprotein data presented strongly suggest that both type 2 and type 4 lipoproteinemia will be found to be related to risk of premature ABI.

Since both the beta and pre-beta lipoprotein fractions contain cholesterol and a high total cholesterol can result from elevations of one or both fractions, it is possible that risk of ABI is primarily a function of the cholesterol level no matter how it is transported or whatever the metabolic basis for its being elevated. This seems to be the case in CHD, as well as ABI.

These observations relate to ABI which is responsible for 60% of strokes and do not apply to intracerebral hemorrhage, cerebral embolus or subarachnoid hemorrhage which, as a group, are in no way related to serum cholesterol level, even in young men. They are based on rather limited data since the excess risk of ABI is confined to premature stroke in those under 55 years. While further follow-up will yield more cases of stroke in the Framingham cohort, there will be, obviously, only two or three more strokes under age 55 evolving in this closed cohort. It will take a larger study of younger subjects followed for a longer period to provide more data. It does not seem likely that this will be forthcoming in the near future — hence, the rather detailed analysis of these meager data.

The decreasing impact of lipid in ABI with advancing age is quite consistent with the findings in coronary heart disease, the major clinical manifestation of atherogenesis. The difference between the two, of course, lies in the fact that men under age 55 seldom have a stroke and when they do it is less likely to be an ABI than some other form of stroke, whereas CHD in men under age 55 is a major cause of death. Thus, the public health implications of lipids are trivial where ABI is concerned and loom large for CHD. However, it must be recognized that ABI is part of a larger problem of cardiovascular disease. The same set of risk factors will identify a tenth of the population from which 25% of the coronary disease, 40% of the occlusive peripheral arterial disease and 50% of the ABIs will emerge. By implication, measures taken to correct these contributors to prevent atherosclerotic brain infarction could (if effective) yield the considerable bonus of a decreased risk of coronary and occlusive peripheral arterial disease.

The atherogenic contributors to ABI are as much a matter of degree as kind. Although hypertension clearly predominates, the excess risk in hypertensives is not uniform and other factors markedly influence the risk associated with any level of blood pressure. The biological factors implicated in atherogenesis, including blood pressure and blood lipids, are graded characteristics continuously distributed without bimodality to denote where normality ends and abnormality begins. Concerning atherogenesis, the common practice of arbitrarily defining only those values outside the usual range as "abnormal" is inappropriate since this is far from the optimal value. Most atherosclerotic disease arises from within the usual distribution of lipid values in the U.S. population which there is reason to believe is uniformly elevated, compared to areas characterized by a low incidence of atherosclerotic disease.

The last word has definitely not been written concerning the role of lipids in atherogenesis in general and ABI in particular. Concepts remain fluid as an intensive search continues for a firm foundation for the management of lipid disorders. Still to be unraveled are questions concerning the optimal range of lipid values, criteria for specific lipid disorders, the lipid most basic to atherogenesis, exactly why the lipid becomes incorporated in atheromata, and the determinants of the generally high lipid values encountered in the U.S.A.

While a simple casual cholesterol determination may be the only lipid determination required to assess risk of atherosclerotic disease, knowledge of the lipoprotein pattern may be helpful in selecting the most efficacious management of hyperlipidemia. It is clear that a substantial reduction in mortality will require that vulnerable persons in the general population be detected and placed under vigorous, sustained long-term prophylactic management and surveillance. The background of the potential candidate has been elucidated and a profile capable of estimating risk over a wide range has been devised. Although less so for ABI, serum lipid is nevertheless a potent contributor to other atherosclerotic disease such as coronary disease and this must be taken into account.

References

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