Abstract. Objectives: To determine the correlation between cardiovascular risk calculated using the Framingham equation and the circulating levels of 4 ‘emerging’ predictors of vascular events: fibrinogen (Fib), lipoprotein (a) (Lp(a)), albumin (Alb) and bilirubin (Bil) (F-L-A-B). Patients and Methods: A retrospective survey was carried out using patients referred to a specialist university-based clinic. A total of 376 patients with primary dyslipidaemia (209 men), without overt vascular disease, had their cardiovascular risk estimated using the Framingham equation. Results: Among the men, smokers (n=45) were significantly younger (p=0.014) than non-smokers (n=164). Smokers when compared with non-smokers had significantly higher median Fib levels (3.84 (1.15-5.87) vs. 3.08 (1.44-5.47) g/l; p<0.0001) and lower median Bil levels (8 (3-17) vs. 10 (1-28) Ìmol/l; p=0.016). When non-smoker men without clinically evident vascular disease were considered, there was a significant positive Fib and negative Alb correlation with calculated risk, whether the family history was considered or not. Moreover in smokers, the only significant correlation was a negative one between Bil and cardiovascular disease risk. Lp(a) correlated with risk for stroke in women non-smokers whether the family history was considered or not, while Alb correlated with risk for stroke in women non-smokers without family history. Conclusion: Fib, Lp(a), Alb and Bil (F-L-A-B) may be predictors of vascular events in high-risk populations. Prospective studies should evaluate whether the F-L-A-B markers are useful in the assessment of cardiovascular risk load. Such an advantage would make treatment more cost effective by improving patient targeting. The F-L-A-B markers could eventually become targets for new drugs.

Several modifiable vascular risk factors have been identified. Among the more ‘established’ are hypertension, smoking, dyslipidaemia and diabetes mellitus (1-3). However, there is a need to identify ‘new’ predictors of vascular events to further improve the selection of high-risk patients. Furthermore, some currently available drugs aimed at major risk factors also exert beneficial or hostile effects on other variables that may predict vascular risk (4-7). This information may influence the choice of medication.

Fibrinogen (Fib) is involved in clotting, activates platelets and increases blood viscosity (8); Fib degradation products promote atherogenesis. Several large studies showed that Fib is a powerful and independent predictor of a wide range of vascular pathology (e.g. myocardial infarction, stroke and progression of carotid or peripheral arterial disease) (9-14). The lipoprotein (a) (Lp(a)) molecule includes low-density lipoprotein cholesterol (LDL-C) which is involved in the process of atherogenesis (15). In addition, Lp(a) shares some structural homology with plasminogen (16) and may therefore inhibit fibrinolysis (17). However, epidemiological surveys have not consistently shown a link between elevated serum Lp(a) levels and an increased incidence of cardiovascular disease (CVD) (12, 18-21).

Both albumin (Alb) (22, 23) and bilirubin (Bil) (24-25) are antioxidants that may act in combination. Epidemiological studies have shown that low serum Alb levels are associated with increased mortality from CVD (22, 26). The same may apply to serum Bil levels (27-32).
In the present retrospective study, we evaluated the relationship between cardiovascular risk (derived using the Framingham equation) (1) and the circulating levels of 4 'emerging' predictors of vascular events: Fib, Lp(a), Alb and Bil (F-L-A-B) in patients attending a vascular disease prevention clinic.

Patients and Methods

Patient selection. The records of 376 consecutive primary prevention patients (209 men) had their cardiovascular risk estimated using the Framingham equation. In order to create a more homogeneous patient group, the following exclusion criteria were applied: i) Therapy with any lipid-lowering agent during the previous 4 months; ii) Fasting serum glucose (Glu) concentration above 5.0 mmol/l with abnormal oral glucose tolerance test (oGTT); iii) Abnormal liver function tests: Reference ranges for tests were: aspartate aminotransferase (AST)=5-40 µ/l; alanine aminotransferase (ALT)=5-40 µ/l; gammaglutamyl transferase (GGT)=10-48 µ/l; alkaline phosphatase (ALP)=35-130 µ/l; albumin (Alb)=35-55 g/l; bilirubin (Bil)=3-17 µmol/l (values up to 25 µmol/l were allowed provided all the other liver function tests were normal). Thus, we did not exclude subjects who show a small rise in serum Bil as a result of fasting; iv) Abnormal renal function: Reference ranges were: urea=3.0-6.5 mmol/l (values up to 7.5 mmol/l were allowed for those above the age of 70 years); creatinine=60-120 µmol/l; sodium=135-145 mmol/l; potassium=3.5-5.0 mmol/l; v) Abnormal thyroid function tests: Reference ranges were: TSH=0.5-4.7 mU/l; free thyroxine=10-25 pmol/l; vi) Declared or determined history of alcohol or other drug abuse. For alcohol consumption, the limits were set at 21 units/week for men and 14 units/week for women; vii) Psychiatric conditions, whether involving medication or not; viii) Chronic inflammatory disease (e.g. rheumatoid arthritis, Crohn's disease, ulcerative colitis, collagen diseases) or cancer (fibrogen), and in some circumstances Lp(a), can act as acute phase proteins (10, 20); ix) Recent (within 3 months) major cardiovascular or other illness, angioplasty or surgery; x) Treatment with retinoic acid (e.g. phototherapy therapy or oral contraceptives), progestins, fish oils or cyclosporine, since these drugs may exert effects on lipids and possibly fibrinogen levels (33-35); xi) Current or recent (within 4 months) pregnancy.

Smoking status. Non-smokers were defined as those who had never smoked or who quit 6 or more months before sampling. A 6-month period was selected to allow time for reversal of as many variables as possible within a practical time frame. Patients who had quit for less than 6 months were not included in this study.

Clinical and laboratory investigations

Collection of samples. All samples were collected in the morning after fasting for a minimum of 12 h with water only allowed.

Lipid profile. Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were assayed by standard enzymatic methods (Boehringer Mannheim, Sussex, England) adapted for the Hitachi 911 analyser (HDL was measured after precipitating apolipoprotein B using phosphotungstate). The serum LDL-C was calculated using the Friedewald formula except for samples (n=22) with serum TG above 4.5 mmol/l, for which HDL-cholesterol could not be determined with the method used. Non-HDL-C was calculated using the equation TC-HDL-C. Serum Lp(a) concentrations were measured using an enzyme-linked immunosorbent assay (Immuno Ltd., Kent, England).

Plasma Fib. Samples were collected in trisodium citrate (1 ml 3.8% trisodium citrate + 9 ml blood) and measured using the Clauss method (clotting activity) using an autoanalyser (ACL 300 Research; IL Labs., Warrington, UK), as previously described (36).

Serum Alb. This was measured using dye binding method with bromocresol green (Boehringer Mannheim, Sussex, England) adapted for the Hitachi 911 analyser.

Serum Bil. This was measured using a diazo method (Boehringer Mannheim, Sussex, England) adapted for the Hitachi 911 analyser.

Liver and renal function profiles and serum glucose concentration. These were all determined by standard methods in routine use in our department.

The Department of Chemical Pathology and Human Metabolism, Royal Free Hospital participates in several quality assurance programs (including schemes for Lp(a) and Fib) and has full Clinical Pathology Accreditation (CPA).

Calculation of cardiovascular risk using the Framingham equation [www.bhsoc.org]. The Framingham equation can only be used to calculate cardiovascular risk in the absence of CVD (primary prevention) in either gender. The equation can derive coronary heart disease (CHD), stroke risk and overall CVD risk. This equation has an age limitation (32 to 74 years). To increase the number of patients, those aged 30-31 years were entered as 32-year-olds. Similarly, patients aged 75-77 years were entered as 74-year-olds for the estimation of the Framingham risk. The following variables are considered in the equation: age, gender, systolic blood pressure, serum TC and HDL-C levels, smoking status and the presence/absence of diabetes mellitus or left ventricular hypertrophy based on ECG criteria. We analysed the results using the Framingham calculation with and without considering a positive family history. A positive family history was considered to add 50% to the overall risk.

Statistical analysis and presentation of results. Values are expressed as median and range. All p values are two-tailed. Between-group results were compared using Mann-Whitney tests. Correlations between cardiovascular risk and Fib, Lp(a), Alb and Bil levels were assessed with Spearman's correlation (r). Smokers and non-smokers were considered separately in both genders because smoking is known to raise plasma Fib levels (37, 38) and there is an association between smoking and reduced circulating levels of Alb (22, 26) and Bil (29, 31, 39, 40). Smoking does not appear to affect serum Lp(a) levels (41, 42).

Results

Patient characteristics. The characteristics of the 376 patients enrolled in this survey are listed in Table I.

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Differences between smokers and non-smokers. Among the men, smokers (n=45) were significantly younger (p=0.014) than non-smokers (n=164) (Table I). Smokers when compared with non-smokers had significantly higher median Fib levels (p<0.0001) and lower median levels of Bil (p=0.016). The median plasma levels of Lp(a) and Alb among smoker and non-smoker men were not significant.

There were no significant differences in the F-L-A-B markers between smoking (n=19) and non-smoking (n=148) women possibly because of the small numbers in the smoking group.

Gender differences. Because of the difference in age between men and women, we randomly matched 95 pairs of non-smoking men and women (all without CVD) (Table II). Women had significantly higher median plasma Fib (p=0.02), TC (p<0.0001), HDL-C (p<0.0001), LDL-C (p=0.001) and non-HDL (p=0.013) levels compared with men. In contrast, TG and Bil levels were significantly higher in men (p=0.009 and p=0.003, respectively).

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We did not match the smokers according to gender because of the small numbers (Table I).
Correlations between F-L-A-B variables and risk calculated using the Framingham equation, with and without considering the family history. We do not report any correlation in the female smokers, because the small number (n=19) included in this group may yield spurious results.

**Correlation between Fib levels and calculated risk.** Male non-smokers (n=149): there was a significant correlation between Fib and risk of CHD, stroke and CVD without considering the family history of vascular disease (Table III). Similar results were obtained when the family history was considered in male non-smokers (n=142) although the correlation tended to be weaker.

Female non-smokers with (n=144) and without (n=143) considering the family history: there was a significant correlation between Fib and risk for CHD, stroke and CVD.

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**Table III. Correlations (rs) of Fib, Lp(a), Alb and Bil with the CVD risk (CHD and stroke) calculated using the Framingham equation in men and women without CVD.**

<table>
<thead>
<tr>
<th></th>
<th>CHD risk</th>
<th>Stroke risk</th>
<th>CVD risk</th>
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<tbody>
<tr>
<td></td>
<td>rs</td>
<td>p</td>
<td>rs</td>
</tr>
<tr>
<td>a) Men: non-smokers (n=164)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fib (g/l)</td>
<td>[A] (n=149)</td>
<td>0.30</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>[B] (n=142)</td>
<td>0.25</td>
<td>0.003</td>
</tr>
<tr>
<td>Lp(a) (g/l)</td>
<td>[A] (n=127)</td>
<td>-0.14 NS</td>
<td>-0.10 NS</td>
</tr>
<tr>
<td></td>
<td>[B] (n=123)</td>
<td>-0.14 NS</td>
<td>-0.10 NS</td>
</tr>
<tr>
<td>Alb (g/l)</td>
<td>[A] (n=136)</td>
<td>-0.27</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>[B] (n=131)</td>
<td>-0.22</td>
<td>0.01</td>
</tr>
<tr>
<td>Bil (μmol/l)</td>
<td>[A] (n=136)</td>
<td>0.010</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>[B] (n=131)</td>
<td>0.03</td>
<td>NS</td>
</tr>
</tbody>
</table>

[A]: Not including family history in the risk calculation, [B]: including family history in the risk calculation, NS: not significant, CHD: coronary heart disease, CVD: cardiovascular disease. For the rest of abbreviations, see Table I.

<table>
<thead>
<tr>
<th></th>
<th>CHD risk</th>
<th>Stroke risk</th>
<th>CVD risk</th>
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<tr>
<td>b) Women: non-smokers (n=148)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fib (g/l)</td>
<td>[A] (n=144)</td>
<td>0.22</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>[B] (n=143)</td>
<td>0.19</td>
<td>0.02</td>
</tr>
<tr>
<td>Lp(a) (g/l)</td>
<td>[A] (n=136)</td>
<td>0.09</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>[B] (n=135)</td>
<td>0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Alb (g/l)</td>
<td>[A] (n=138)</td>
<td>-0.07</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>[B] (n=137)</td>
<td>-0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Bil (μmol/l)</td>
<td>[A] (n=141)</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>[B] (n=140)</td>
<td>0.02</td>
<td>NS</td>
</tr>
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</table>

[A]: Not including family history in the risk calculation, [B]: including family history in the risk calculation, NS: not significant, CHD: coronary heart disease, CVD: cardiovascular disease. For the rest of abbreviations, see Table I.

<table>
<thead>
<tr>
<th></th>
<th>CHD risk</th>
<th>Stroke risk</th>
<th>CVD risk</th>
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<tbody>
<tr>
<td>c) Men: smokers (n=45)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fib (g/l)</td>
<td>[A] (n=42)</td>
<td>0.26</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>[B] (n=42)</td>
<td>0.22</td>
<td>NS</td>
</tr>
<tr>
<td>Lp(a) (g/l)</td>
<td>[A] (n=40)</td>
<td>-0.13</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>[B] (n=40)</td>
<td>-0.17</td>
<td>NS</td>
</tr>
<tr>
<td>Alb (g/l)</td>
<td>[A] (n=43)</td>
<td>0.12</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>[B] (n=43)</td>
<td>0.14</td>
<td>NS</td>
</tr>
<tr>
<td>Bil (μmol/l)</td>
<td>[A] (n=45)</td>
<td>-0.39</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>[B] (n=42)</td>
<td>-0.32</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Fib: fibrinogen; Lp(a): lipoprotein (a); Alb: albumin; Bil: bilirubin; TC: total cholesterol; TG: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol, NS: not significant.
Correlation between $L_p(a)$ levels and calculated risk. There were no significant correlations between $L_p(a)$ levels and vascular risk in any group except for stroke in women non-smokers, whether the family history was considered or not (Table III).

Correlation between Alb levels and calculated risk. In male non-smokers with ($n=136$) and without ($n=131$) considering the family history, there was a significant negative correlation between Alb and the risk of CHD, stroke and CVD. In female non-smokers, a significant negative correlation was only seen when the family history was not considered ($n=137$).

Correlation between Bil levels and calculated risk. In male smokers there was a significant negative correlation between Bil and CHD risk, risk for stroke and CVD risk whether the family history was considered ($n=43$) or not ($n=42$). There were no significant correlations in the other groups (Table III).

Discussion

We showed that in patients without overt CVD, referred to a specialist lipid clinic, plasma Fib levels were higher in men who smoked compared with those who did not. Furthermore, in the age-matched analysis of non-smokers, women had significantly higher Fib levels than men. However, among men, the smokers were significantly younger ($p=0.014$) than the non-smokers. We did not adjust the ages in these two groups because Fib tends to rise with age (43). Therefore, the age effect would be against finding a significant difference. Similar relationships for Fib were reported in other populations (40, 44, 45). The agreement with previous findings both validates our results and extends the evidence for Fib to a dyslipidemic population without CVD referred to a lipid clinic.

The significant correlation between Fib levels and vascular risk for CHD, stroke and CVD in non-smokers is in line with the evidence showing that the circulating levels of this coagulation factor are associated with subclinical atherosclerosis (37, 46, 47). Thus, patients with high vascular risk are expected to have more extensive subclinical atherosclerosis. The lack of a similarly significant correlation between Fib levels and vascular risk in smokers may reflect the adverse effect of smoking on Fib levels, which could mask a relationship with vascular risk. The correlation between Fib levels and vascular risk whether family history was included or not, did not differ markedly. In this context, it is relevant that the role of Fib-related genes in predicting vascular risk has recently been questioned (48).

Whether measuring Fib levels improves the estimation of overall vascular risk remains to be established (48, 49). Similarly, it is not clear if lowering plasma Fib levels (e.g. pharmacologically) will reduce vascular risk. This question may never be definitively answered because currently available medication that can lower plasma Fib levels also modifies other risk factors (e.g. lipids, blood pressure or inflammation) (4, 6, 50-52).

We did not find any differences in $L_p(a)$ levels when considering the effect of smoking or gender. Smoking has not been shown to affect $L_p(a)$ levels (42, 53). $L_p(a)$ levels are only slightly influenced by age in men (41, 42). In the Northern Sweden WHO MONICA project (54), there was a weak but significant correlation between $L_p(a)$ and age in both men and women. In PROCAM (55), there was a weakly positive correlation between $L_p(a)$ and age only in healthy women. This age-dependent change in women was related to the rise in serum $L_p(a)$ after the menopause (54, 56, 57). Because the median age of the women in the age-matched group analysis was 57 years, we would expect the observed trend for higher $L_p(a)$ values compared with men. This 37.5% difference did not achieve significance probably because of the small number of patients compared and the wide range of the $L_p(a)$ values.

Impaired renal function and hypothyroidism can raise serum $L_p(a)$ levels (58, 59). Hormone replacement therapy (HRT) can lower $L_p(a)$ levels (57, 60). We eliminated this variability by excluding patients with hypothyroidism or impaired renal function as well as women on HRT. The effect of diabetes (in the absence of impaired renal function) on $L_p(a)$ levels does not seem to be defined (61). We avoided this controversy by excluding patients with diabetes.

The only significant correlation between $L_p(a)$ and stroke risk was in women non-smokers whether the family history was considered or not. The link between $L_p(a)$ and the risk for stroke was reviewed elsewhere (19, 62, 63). Other studies showed that $L_p(a)$ concentrations are associated with a higher incidence of ischemic stroke in black men and women and white women, but not in white men (64).

Most (>90%) of the variance in $L_p(a)$ levels is genetically determined (65). It follows that it may be difficult to document correlations with risk or differences related to gender or lifestyle (e.g. smoking status). Nevertheless, a correlation between plasma Fib and $L_p(a)$ levels has been reported in several studies, including our own (66). The mechanisms that may mediate such a relationship are discussed elsewhere (66).

Alb showed no significant difference when considering the effect of smoking in either gender or in the age-matched analysis of non-smokers. There is evidence showing that circulating Alb levels are lower in smokers (26). We observed a similar non-significant trend. The lack of significance may be attributed to the small numbers of smokers.
Alb levels correlated negatively with calculated vascular risk (CHD, stroke and CVD) in male non-smokers. The only significant correlation for Alb in women was for stroke in non-smokers when the family history was not considered. The lack of correlation in smokers may reflect the masking of this relationship by an adverse effect of smoking on Alb levels.

Lower levels of serum Alb are associated with increased risk of all-cause (67-69) and cardiovascular mortality (67, 70-73), as well as with CHD (22, 71, 74, 75) and stroke incidence (76, 77).

Several hypotheses have been proposed to account for the strong inverse relationship between serum Alb and CHD, but no consensus has emerged as to whether low serum Alb plays a direct role or if it is merely an indicator of the vascular changes associated with cigarette smoking (26, 78). In one study (ARIC study; 14506 men and women; 5.2 years of follow up) an inverse relationship between Alb and CHD events was seen only in current cigarette smokers (75). In another prospective study of 7690 British men (aged 40-59 years, 16.8 years mean follow-up), a strong significant inverse relationship between serum Alb and major CHD and stroke events and all cause mortality was observed. However, the inverse relationship was seen only in current cigarette smokers and ex-smokers for CHD events and only in current smokers for stroke events (26). Moreover, in a cohort study (79), comprising healthy subjects and patients with acute or chronic illness, serum Alb concentration was inversely related to mortality in a graded manner; the estimated increase in mortality risk for each 2.5 g/l decrement in Alb ranged from 24% to 56% (79). The association predicts overall and cause-specific mortality including cardiovascular mortality. The above finding was confirmed in a prospective study of 7735 men followed for 8 to 10 years (80); for each 2.55 g/l decrement in serum Alb, the odds of death rose by 47%. This relationship was shown to be independent of the others cofactors and the value of serum Alb could be used as a predictor of survival in the general population (80).

In contrast, several observational studies did not find an association between serum Alb and mortality from CVD or CHD (81-83). Low Alb levels are part of the acute phase reaction (84). Furthermore, Alb may attenuate platelet hyperactivity (e.g. induced by Fib) (23, 85) and this protein may act as an antioxidant (22). It is not clear whether a low serum Alb level is a non-specific, prognostic variable, a marker for subclinical disease, or part of the causal mechanism leading to CHD (71).

The combination of low Alb and Bil levels is associated with a greater than expected risk of CHD in men and women (the risk was greater than the additive risks associated with low levels of either Alb or Bil alone) (86).

Men without CVD who smoked had significantly (p=0.016) lower serum Bil levels than those who did not. Male smokers were significantly younger (p=0.014) than non-smokers but we did not adjust their ages, because Bil levels do not change within this age range and the number of smokers was small (87). Smoking was associated with lower serum Bil concentrations in women but this difference was not significant. This pattern was also reported by others (40, 88). Bil levels were significantly higher in men compared with women in the age-matched comparison of non-smokers. This gender-dependent difference has been previously reported in healthy subjects (31, 39, 40, 87, 89).

The duration of smoking is a more important determinant for serum Bil concentrations than the number of cigarettes smoked per day, which may indicate the cumulative negative effects of smoking on the endogenous antioxidant system (88). Smoking may also increase the risk of vascular disease by raising the concentrations of oxidized lipids (90). Serum Bil levels were also significantly lower in untreated hypertensives when compared with normotensives or treated hypertensives (4).

In the Framingham Offspring Study (91), low Bil was associated with an increased risk of myocardial infarction and CVD among men but not women. Furthermore, a case-control study, reported an inverse relation between serum Bil and CVD in men and women (28). The reason for this discrepancy between genders is not clear (86).

Bil levels correlated significantly and inversely with the risk of CHD, stroke and CVD only in male smokers whether a positive family history was present or not. Several studies noted an inverse relationship between the presence of vascular disease and circulating Bil levels (28, 29, 31, 32, 40). In another study, patients with early familial CHD had a total serum Bil of 8.9±6.1 µmol/L compared with 12.4±8.1 µmol/L (p=0.0001) in healthy control subjects (28). Further support for this inverse correlation came from a study which described a genetic variation in Bil concentration, with individuals with early CHD displaying lower Bil than unaffected persons (p<0.01) (92). Low Bil was suggested as an independent risk factor for CHD and an inverse correlation was demonstrated between Bil concentration and CHD morbidity (29, 32, 93, 94). In addition, when comparing serum Bil and Alb concentrations in 3 groups of patients: peripheral vascular disease (PAD), CHD and dyslipidaemia without clinically overt CVD, the levels of Bil and Alb tended to be lower in those with PAD or CHD (40, 95). Not all studies showed a relationship between Bil and increased vascular risk. A prospective study (30) observed 737 major CHD events in 7685 middle-aged men during 11.5 years of follow-up. A U-shaped relationship was found between serum Bil and risk for CHD. Both low and very high levels were associated with an increased risk of CHD relative to intermediate Bil values even after adjusting for other risk factors (30).
Conclusion

Fib, Lp(a), Alb and Bil (F-L-A-B) may be predictors of vascular events in high-risk populations. The predictive value of these variables may depend on the characteristics (e.g. gender or smoking status) of the patient subgroup selected. The design of future studies will need to consider these factors.

Whether considering the F-L-A-B values significantly influences risk evaluation remains to be established in prospective studies. On a more speculative note, the F-L-A-B predictors may become targets for therapeutic intervention.

References


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