Procoagulant activities of plasma factors VIIc and Xc are positively and independently associated with concentrations of the high density lipoprotein apolipoprotein, apo A-II

Maria Atta¹, David Crook², Faria Shafique¹, Desmond G. Johnston¹, Ian F Godsland¹

¹ Endocrinology and Metabolic Medicine, Imperial College London, London, UK.
² Clinical Investigations and Research Unit, Royal Sussex County Hospital, Sussex, UK.

Running title: Apo A-II and factors VII and X

Correspondence to:
Ian F. Godsland, PhD,
Endocrinology and Metabolic Medicine,
Imperial College London,
St Mary’s Campus, Mint Wing,
Praed Street,
London W2 1PG, U.K.
Tel 0044(0)20 7594 3881
Fax 0044(0)20 7886 1790
e-mail i.godsland@ic.ac.uk

full word count: 5335 (2907c Abstract, References, Tables and Figures)
tables: 3
figures: 1
Abstract (232 words)

Background
The pro- and antiatherogenic roles of apolipoproteins B and A-I, respectively, are well-established although the importance of apolipoprotein A-II remains unclear. There is extensive evidence for the involvement of plasma lipoproteins in haemostatic function. However, in vivo studies of relationships between haemostatic variables and apolipoprotein concentrations are very limited.

Methods
Plasma fibrinogen, factors VIIc and Xc (FVIIc and FXc, respectively), apolipoproteins (apo) A-I, A-II and B, triglycerides, total, low density and high density lipoprotein (HDL) cholesterol, and cholesterol in HDL subfractions 2 and 3 were measured in 186 apparently healthy Caucasian men (aged 26-78y; body mass index 19.9-37.8 kg/m²). Associations between haemostatic, apolipoprotein, lipid and lipoprotein variables were explored in uni- and multivariable analyses.

Results
Fibrinogen did not correlate with any of the lipid-related variables. FVIIc and FXc were significant positive univariate correlates of total cholesterol (correlation coefficients 0.26, p<0.001 and 0.19, p<0.05, respectively) triglycerides (0.37, p<0.001 and 0.36, p<0.001), and apoB (0.21, p<0.01 and 0.17, p<0.05) and apoA-II (0.19, p<0.05 and 0.29, p<0.001). HDL₂ subfraction cholesterol correlated negatively with FVIIc and FXc (-0.20, p<0.01 and -0.22, p<0.01, respectively). In multivariable analysis, only the associations of FVIIc and FXc with total cholesterol, triglycerides and apoA-II remained statistically significant.

Conclusions
Total cholesterol and triglycerides were the major independent lipid correlates of FVIIc and FXc. The independent and positive associations of apoA-II with FVIIc and FXc suggest a prothrombotic involvement for this apolipoprotein.
Key words:

apolipoproteins; high density lipoprotein; lipids; apoA-II; Factor VII; Factor X; fibrinogen
Introduction

The importance of lipoproteins and haemostasis in the aetiology of atherosclerosis is well established. Perturbation in the balance between coagulation and fibrinolysis can promote the development of atherosclerosis and a number of studies have shown that disturbances in lipoprotein metabolism can influence this balance \(^1\). Triglycerides and very-low-density lipoprotein (VLDL) elevate Factor VII coagulant activity (FVIIc) and also impair fibrinolysis by increasing plasminogen activator inhibitor 1 (PAI-1) activity \(^2\). Moreover, both VLDL and oxidized low density lipoprotein (LDL) support the assembly of the prothrombinase complex of phospholipids, calcium ions and coagulation factors V, X and II \(^3\). In contrast, the anti-atherogenic lipoprotein, high density lipoprotein (HDL) has both anti-coagulatory and pro-fibrinolytic properties \(^4,5\), perhaps due to an ability to inhibit VLDL-stimulated tissue factor synthesis \(^2\) and activate factor X \(^6,7\).

The principal apolipoproteins of LDL and HDL are apolipoprotein B-100 (apo B-100) and apolipoprotein A-I (apo A-I), respectively and it has been suggested that these might provide better indices of atherosclerosis risk than the lipoprotein cholesterol concentrations \(^8,9\). The importance of the second most prominent HDL apolipoprotein, apolipoprotein A-II (apo A-II), is less clear, with both pro- and anti-atherogenic properties having been described\(^{10,11}\). In vitro studies suggest that the apolipoproteins may have discrete, mainly anti-coagulatory, interactions with the haemostatic system. For example, apo A-I and apo A-II can inhibit activation of Factor X by Factor VII and tissue factor \(^6,12\) and apo A-I inhibits production of the prothrombinase complex by limiting the availability of anionic lipids on extracellular surfaces \(^13\). Moreover, apoB-100 can inhibit tissue factor activation \(^14\). However, in vivo approaches to understanding these relationships appear extremely limited.
The Heart Disease and Diabetes Risk Factors in a Screened Cohort Study (HDDRISC) is an open, occupational cohort study, which has included an unusually detailed range of risk factor measurements. In the present analysis we have investigated relationships between the haemostatic variables fibrinogen, FVIIc and factor X coagulant activity (FXc), the apolipoproteins apo A-I, apo A-II and apoB-100 as well as plasma triglycerides and total, LDL and HDL cholesterol.
Participants and Methods

Design
The Heart Disease and Diabetes Risk Indicators in a Screened Cohort (HDDRISC) Study is a cohort study of metabolic risk factors for the development of coronary heart disease and diabetes\textsuperscript{15,16}. The study began in 1971 as a company health program, in the course of which participants received a range of metabolic, clinical and laboratory measurements. The present analysis concerns the 186 Caucasian male recruits who, between 1994 and 1998, had both apolipoproteins and haemostatic factors measured. Written, informed consent to the study was obtained in each case, and local research ethics committee approval was given.

Procedures
Participants were instructed to have fasted overnight (>12h), to have taken only water and refrained from cigarette smoking on the morning of their test. Height and weight were measured and a clinical history was taken including details of exercise habits, smoking and alcohol consumption. The participants rested for 15 minutes in the semi-recumbent position and their systolic and diastolic blood pressure were recorded using a mercury sphygmomanometer. An indwelling cannula was inserted into an antecubital vein in each arm. Blood samples were taken for fasting plasma measurements. All samples were kept on ice before separation of plasma, which took place within 1 hour of the sample being taken. Samples for routine biochemical measurements were stored at 4°C before analysis. Plasma samples for measurement of haemostatic factors were frozen immediately.

Laboratory Measurements
Plasma levels of fibrinogen, FVIIc and FXc were measured by single-stage clotting assays using human factor VII- or factor X-deficient plasma and recombinant human
tissue factor with coagulant activity quantified by prothrombin time-based nephelometry using reagents and an automated ACL 100 coagulation analyser supplied by Instrumentation Laboratory (Lexington, MA, U.S.A.). Apolipoproteins A-I, A-II and B (predominantly apoB\(_{100}\), since samples were taken in the fasted state) were measured by immunoturbidimetry-based commercial kits (Immuno AG, Vienna, Austria) using a Cobas Mira discrete analyzer (Roche, Basel, Switzerland). Serum total cholesterol, triglycerides, HDL and LDL cholesterol concentrations were measured as described previously \(^{15}\). Concentrations of HDL and HDL subclass 3 (HDL\(_3\)) cholesterol were measured after sequential precipitation with heparin and manganese ions \(^{17}\) and dextran sulfate \(^{18}\), respectively. The serum concentration of HDL subclass 2 (HDL\(_2\)) cholesterol was calculated as the difference between the HDL and HDL\(_3\) cholesterol levels. Quality control was continuously monitored with commercially available lyophilized sera and by participation in national quality-control programs. Between batch assay coefficients of variation were: fibrinogen 7%; FVIIc 7%; FXc 4%; apolipoprotein A-I 3-4%; apolipoprotein A-II 1-3%; apolipoprotein B 2-4%; serum total cholesterol and triglycerides 1-2%; HDL cholesterol 2-4%; HDL\(_3\) cholesterol 5-7%.

**Data analysis**

For entry in correlation and regression analyses, cigarette smoking was categorized as: never smoked/ex-smokers (0), or less than 5 (1), 5-14 (2), 14-24 (3), or more than 24 (4) cigarettes/day. Alcohol intake was expressed as units consumed per week (a unit of alcohol approximates 10 ml or 8 g pure ethanol and is the amount contained in a half-pint (284 ml) of beer, a single glass (125 ml) of table wine, or a single measure (25 ml) of spirits). Exercise habit was expressed as none (0), moderate (1), or aerobic (2). Statistical analyses were carried out using STATA 8 (Stata Corporation, College Station, Texas, USA). Fibrinogen, triglycerides, HDL cholesterol and HDL\(_3\) cholesterol were logarithmically transformed and HDL\(_2\) cholesterol, was square-root transformed to
normalize their distributions. Pearson correlation was used to explore univariate associations between haemostatic and other continuous variables and multiple linear regression was used to confirm the independence of significant associations detected.
Results

The 186 participants had a mean age of 49.4 years (range 26-78 years) and a mean BMI of 26.3 kg/m² (range 19.9-37.8 kg/m²). All participants were free of diabetes (maximum fasting plasma glucose 6.1 mmol/l) and cardiovascular disease. Eighty-six percent of participants (n=159) had never smoked or were ex-smokers at the time of testing. Eighty-two percent of participants took no alcohol or described themselves as light irregular drinkers. Eighteen percent drank regularly up to 28 U/wk and only a single individual drank more than 28 U/wk. Forty-four percent of participants did not exercise at all whereas 41% were engaged in moderate exercise and 16% took aerobic exercise. Two individuals were taking lipid-lowering agents (both statins), 11 were taking blood pressure-lowering agents and 3 uric-acid lowering agents. Two individuals reported regular aspirin use. Median and interquartile ranges for study variables are shown in Table 1.

The strongest univariate correlate of fibrinogen (Table 2) was age (p<0.001) with cigarette smoking also a positive correlate (p<0.05). In contrast, neither FVIIc nor FXc were significantly related to age or cigarette smoking. FVIIc and FXc were, however, strongly positively correlated with BMI and also with systolic and diastolic blood pressure and were negatively correlated with exercise. In contrast, fibrinogen was only weakly associated with BMI, showed weaker correlations with blood pressure and did not correlate with exercise. Fibrinogen and FXc, but not FVIIc, were positively correlated with alcohol intake.

Fibrinogen did not correlate with any of the lipid or lipoprotein-related variables (Table 2). Both FVIIc and FXc were positively correlated with apo B, apo A-II, total cholesterol and triglycerides and were negatively correlated with HDL₂ cholesterol. Neither FVIIc nor FXc correlated with apo A-I, LDL cholesterol or HDL₃ cholesterol. Median FVIIc
and FXc in successive tertiles of apo A-II concentration are illustrated in Figure 1. On analysis of variance there was, as expected from the correlations described above, significant variation between tertiles of FVIIc (p=0.01) and FXc (p=0.001). Mean FVIIc and FXc in the two upper tertiles of apo A-II both differed significantly from the mean in the lowest tertile (FVIIc: p= 0.02 and p=0.009, respectively; FXc: p=0.01 and p=0.0004, respectively). Mean FVIIc and FXc did not differ significantly between the two upper tertiles of apo A-II (p=0.7 and p=0.3, respectively).

In multiple linear regression analysis, with age, BMI, alcohol intake, exercise habit and current smoking included as predictor variables (Table 3), apo A-II, total cholesterol and triglycerides remained significant predictors of both FVIIc and FXc, whereas HDL₂ cholesterol and apo B ceased to be significant. With age, BMI, alcohol intake, exercise habit and current smoking included, there was a 3- to 4-fold reduction in the magnitude of the regression coefficient for HDL₂ cholesterol as a predictor of FVIIc and FXc. In further multiple regression analyses (results not shown) this reduction in the magnitude of the regression coefficients was found to be almost entirely due to the effect of BMI and an even greater reduction was seen with inclusion of triglycerides in the model in place of BMI. BMI and triglycerides predicted FVIIc and FXc independently of one another.
Discussion

A number of previous studies have explored relationships between haemostatic factors and lipoprotein concentrations and a few have included measurements of both haemostatic factors and apo A-1 and apo-B \(^{19,22}\). However, in these studies, apolipoproteins have generally been evaluated as cardiovascular risk markers, and there remains relatively little information on their relationships with haemostatic factors. The present study is, to the best of our knowledge, the first in humans \textit{in vivo} to examine specifically relationships between haemostatic factors and a range of the principal apolipoproteins that includes apo A-II. We found positive associations between apo B and apo A-II and FVIIc and FXc, but only the associations with apo A-II were fully independent. It was also noteworthy that total cholesterol and triglycerides were independently associated with FVIIc and FXc and that fibrinogen showed no associations with variables related to lipid metabolism. These findings were made in a group of apparently healthy Caucasian males, free of diabetes and cardiovascular disease and at relatively low risk of developing these conditions. Whether they are equally present in women, other ethnic groups or in at-risk or disease states remains to be established.

Our principal novel finding is the independent, positive \textit{in vivo} association between apo A-II and FVIIc and FXc. For FXc, this contrasts with the relationship that would expected on the basis of the \textit{in vitro} demonstration that apo A-II can inhibit factor X activation \(^{6,12}\). Nevertheless, there are several potential explanations for the positive relationship we observed. For example, a specific property of apo A-II that could affect FVIIc and FXc is its ability to displace the antioxidant enzyme paraoxonase from HDL particles \(^{23}\) and render them proinflammatory \(^{24}\). Paraoxonase protects LDL from lipid peroxidation \(^{25}\) and increased LDL oxidation can reduce the activity of LDL-bound tissue factor pathway inhibitor \(^{14,26}\). This would be expected to increase the activation
of the extrinsic pathway and increase FVIIc and FXc. Simultaneous measurement of lipid peroxidation, paraoxonase activity, apolipoproteins and haemostatic factors will be needed to explore whether these relationships are mediating the association between apo A-II and FVIIc and FXc.

Insulin resistance could be a common factor linking apo A-II with FVIIc and FXc. We have previously reported positive associations between insulin resistance and FVIIc and FXc in this cohort 27 and a number of reports describe links between insulin resistance and apo A-II. Mice overexpressing apo A-II have increased insulin resistance 28 and the converse is true of mice under-expressing apo A-II 29. Against this, mice over-expressing human as opposed to murine apo A-II do not appear to become insulin resistant in response to an atherogenic diet 30. However, there is evidence for links between apo A-II and the insulin resistant state of diabetes 31, including a positive feedback cycle between increased apo A-II production and the metabolic disturbances of diabetes 32. Simultaneous measurement of insulin sensitivity, apolipoproteins and haemostatic factors will be needed to confirm whether or not insulin resistance is mediating the association between apo A-II and FVIIc and FXc.

Another potential explanation for associations between apo A-II and FVIIc and FXc might be found in links between haemostasis and triglyceride metabolism. In vitro studies indicate that apo A-II can suppress lipolysis of VLDL and consequently increase triglyceride concentrations 33, 34. A positive association between triglyceride levels and the activity of vitamin K-dependent clotting factors, including FVIIc and FXc, has been recognised for many years 35 and the role of high VLDL concentrations and consequently high triglyceride levels in the activation of factor VII is well-established 36. Activation of FVIIc and FXc by lipoproteins has been most strikingly demonstrated in the postprandial state 37 and there are reports that a polymorphism in the apo A-II gene
promotor associated with lower levels of apo A-II is also associated with reduced postprandial triglyceride-rich lipoprotein metabolism. The association we found between apo A-II and FVIIc and FXc was independent of accompanying triglyceride concentrations, suggesting that triglyceride-rich lipoprotein metabolism is not the common factor between the positive association we observed between apo A-II and FVIIc and FXc. However, it is possible that the measurements we made did not encompass aspects of postprandial triglyceride metabolism that might still have a mediating role, for example remnants of triglyceride-rich lipoprotein metabolism.

Simultaneous measurement of triglyceride-rich lipoproteins, apolipoproteins and haemostatic factors in the postprandial state will be needed to confirm whether postprandial triglyceride metabolism can mediate the association between apo A-II and FVIIc and FXc.

Activation of factor VII by VLDL appears to be mediated by increased availability of phospholipids and this also appears to be important in the activation of factor X. Apo A-II can directly stimulate ATP binding cassette transporter 1 (ABCA1)-mediated efflux of phospholipids and free cholesterol, which could contribute to activation of factors VII and X and the positive association we observed between apo A-II and FVIIc and FXc. Another possible connection might be the ability of peroxisome proliferator-activated receptor-α to upregulate both ABCA1 expression and apo A-II gene transcription. However, these potential mechanisms derive from animal studies and apply equally to apo A-I and we found no relationship between apo A-I and FVIIc and FXc. Although traces of apo-AII may be synthesised in the intestine, the majority appears to be synthesised in the liver. Hepatic metabolism could play a role in the associations we observed and, in contrast to previous studies, a positive relationship between liver steatosis and apo A-II has now been reported in patients with chronic hepatitis C. However, liver disease tends to be associated with low levels of activated factor VII.
As yet, therefore, there is no definitive mechanism linking apo A-II levels with FVIIc and FXc although there remains the possibility that, rather than apo A-II affecting FVIIc and FXc, these coagulation factors are affecting apo A-II levels. Genetic polymorphisms were not evaluated in our study. Nevertheless, this possibility could be explored in further studies in relation to genetic variation at residue 353 of factor VII which, in the Arg353 variant, is associated with both higher factor VII antigen levels and higher FVIIc. Investigation of this possibility would be complex, however, given the marked interaction between factor VII genotype and triglyceride concentrations and the associations mentioned above between triglyceride metabolism and apo A-II.

It is important to note that our novel findings with regard to apo A-II are supported by our confirmation of other associations previously reported by others. These include the positive associations of FVIIc and FXc with total cholesterol and triglycerides but not with LDL or HDL. Also in agreement with our findings with regard to fibrinogen some previous studies found no significant associations between fibrinogen and serum lipids and lipoproteins. However, in large population studies, fibrinogen has been weakly and positively associated with total and LDL cholesterol, and weakly and negatively associated with HDL cholesterol. It is possible that similarly weak associations are present in the cohort we studied, but larger numbers would have been needed to demonstrate them as significant.

In contrast to the negative association expected from \textit{in vitro} studies, we found a positive association between apo B and FVIIc and FXc. We also found a negative relationship between HDL\textsubscript{2} cholesterol and haemostatic factor activities, but no association with the principal apolipoprotein of HDL\textsubscript{2}, apo A-I. Both the associations of apo B and HDL\textsubscript{2} cholesterol with haemostatic factors ceased to be significant after the adjustment of BMI or triglycerides. Triglyceride-rich lipoproteins, including VLDL,
contain apo B and HDL\textsubscript{2} cholesterol is strongly inversely related to triglycerides. On the basis of these findings, we would maintain that the well-established effect of VLDL and triglycerides on FVIIc and FXc underlies the associations we observed between apo B and HDL\textsubscript{2} cholesterol and haemostatic factors. Further analysis showed that BMI predicted FVIIc and FXc independently of triglycerides, which accords with additional roles for adiposity in haemostasis beyond its accompanying high VLDL and triglyceride levels.

In summary, we found no evidence for strong associations between lipid-related variables and fibrinogen. Neither were there significant, independent, relationships between apo A-1, HDL and HDL subfraction cholesterol concentrations and haemostatic variables. Significant associations between apolipoproteins and haemostatic factors nevertheless extend to apo B and apo A-II and FVIIc and FXc but of these only the associations with apo A-II were independent of age, BMI and lipid and lipoprotein cholesterol concentrations. The mechanism for this association is, at present, unclear.
Acknowledgements

This study received financial support from The Heart Disease and Diabetes Research Trust and The Atherosclerosis Research Trust. The late Professor Victor Wynn initiated and established the HDDRISC study. Since it began, the study has been sustained by many clinical, scientific, technical, nursing and administrative staff, to each of whom we extend our thanks, in particular Mandeep Sidhu for performance of the haemostatic factor measurements.

No conflicts of interest declared
References


Table 1. Group characteristics (median and interquartile range) for 186 apparently healthy Caucasian males

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (IQ range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>49.3 (43.7-56.0)</td>
</tr>
<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>26.0 (24.2-28.1)</td>
</tr>
<tr>
<td>systolic BP (mmHg)</td>
<td>125 (115-135)</td>
</tr>
<tr>
<td>diastolic BP (mmHg)</td>
<td>80 (75-85)</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>272.5 (234-313)</td>
</tr>
<tr>
<td>Factor VII (%)</td>
<td>115.5 (98-129)</td>
</tr>
<tr>
<td>Factor X (%)</td>
<td>113.0 (103-126)</td>
</tr>
<tr>
<td>apolipoprotein B (mg/dl)</td>
<td>77.0 (64-90)</td>
</tr>
<tr>
<td>apolipoprotein A1 (mg/dl)</td>
<td>119 (109-134)</td>
</tr>
<tr>
<td>apolipoprotein A-II (mg/dl)</td>
<td>39 (36-43)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.30 (4.69-6.03)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.39 (0.91-2.08)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.27 (2.65-3.94)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.26 (1.08-1.51)</td>
</tr>
<tr>
<td>HDL$\text{\textsubscript{2}}$ cholesterol (mmol/l)</td>
<td>0.41 (0.29-0.58)</td>
</tr>
<tr>
<td>HDL$\text{\textsubscript{3}}$ cholesterol (mmol/l)</td>
<td>0.83 (0.73-0.93)</td>
</tr>
</tbody>
</table>
Table 2. Univariate Pearson correlations (R) between individual characteristics, lipids, lipoproteins and apolipoproteins and haemostatic factors

<table>
<thead>
<tr>
<th></th>
<th>Fibrinogen*</th>
<th>Factor VIIc</th>
<th>Factor X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.32&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-0.05</td>
<td>-0.05</td>
</tr>
<tr>
<td>BMI</td>
<td>0.14&lt;sup&gt;0.05&lt;/sup&gt;</td>
<td>0.33&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.30&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.02</td>
<td>0.13&lt;sup&gt;0.08&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.05</td>
<td>0.15&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Exercise</td>
<td>-0.12</td>
<td>-0.14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.14&lt;sup&gt;0.05&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.16&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.24&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.17&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.05</td>
<td>0.28&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.16&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>0.09</td>
<td>0.21&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.17&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>-0.01</td>
<td>-0.04</td>
<td>-0.02</td>
</tr>
<tr>
<td>Apolipoprotein A-II</td>
<td>-0.10</td>
<td>0.19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.29&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.02</td>
<td>0.26&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.19&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Triglycerides&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-0.01</td>
<td>0.37&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.36&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.01</td>
<td>0.12&lt;sup&gt;0.09&lt;/sup&gt;</td>
<td>0.05</td>
</tr>
<tr>
<td>HDL cholesterol&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-0.05</td>
<td>-0.11</td>
<td>-0.10</td>
</tr>
<tr>
<td>HDL&lt;sub&gt;2&lt;/sub&gt; cholesterol&lt;sup&gt;†&lt;/sup&gt;</td>
<td>-0.07</td>
<td>-0.20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.22&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>HDL&lt;sub&gt;3&lt;/sub&gt; cholesterol&lt;sup&gt;†&lt;/sup&gt;</td>
<td>-0.02</td>
<td>0.07</td>
<td>0.13&lt;sup&gt;0.06&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Significances: a p<0.05; b p<0.01; c p<0.001. Borderline significances (p<0.1) are also given

* log transformed data

† square-root transformed data
Table 3. Univariate regression coefficients for prediction of Factor VII and X activities by lipids, lipoproteins and apolipoproteins that were significant correlates of FVIIc and FXc, and multivariate regression coefficients for lipids, lipoproteins and apolipoproteins plus the potential confounding factors age, body mass index (BMI), cigarette smoking, alcohol intake and exercise habit as predictors.

<table>
<thead>
<tr>
<th>dependent variable</th>
<th>predictor variable</th>
<th>univariate regression coefficient (lipid-related predictors alone)</th>
<th>multivariate regression coefficient (lipid-related predictors plus age, BMI, smoking, alcohol and exercise)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VII</td>
<td>Apolipoprotein B</td>
<td>0.27&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Apolipoprotein A-II</td>
<td>0.80&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.61&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Total cholesterol</td>
<td>6.38&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.78&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Triglycerides&lt;sup&gt;*&lt;/sup&gt;</td>
<td>15.58&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12.02&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>HDL&lt;sub&gt;2&lt;/sub&gt; cholesterol†</td>
<td>-28.79&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-7.19</td>
</tr>
<tr>
<td>Factor X</td>
<td>Apolipoprotein B</td>
<td>0.15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Apolipoprotein A-II</td>
<td>0.84&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.62&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Total cholesterol</td>
<td>3.19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.55&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Triglycerides&lt;sup&gt;*&lt;/sup&gt;</td>
<td>10.19&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.14&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>HDL&lt;sub&gt;2&lt;/sub&gt; cholesterol†</td>
<td>-22.03&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-8.73</td>
</tr>
</tbody>
</table>

Significances: a p<0.05; b p<0.01; c p<0.001.

<sup>*</sup> log transformed data

† square-root transformed data
Legend to Figure 1

Medians and inter-quartile ranges for Factor VII and Factor X coagulant activity in successive tertile ranges of apolipoprotein A-II (apo A-II) concentration.
Factor VII

Factor X

apo A-II tertile range (mg/dl)

coagulant activity (%)

n of participants

26-36 37-42 43-63
63 69 54

26-36 37-42 43-63
63 69 54