Treatment With Hydroxymethylglutaryl-Coenzyme A Reductase Inhibitors in Hypercholesterolemia Induces Changes in the Components of the Extrinsic Coagulation System

Per Morten Sandset, Henrik Lund, Jon Norseth, Ulrich Abildgaard, and Leiv Ose

The present study was performed to determine the influence of pharmaceutical intervention on parameters of blood coagulation and fibrinolysis in hypercholesterolemic patients. Eighteen otherwise-healthy individuals with heterozygous familial hypercholesterolemia were treated with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (simvastatin, 40 mg daily) for 12–14 weeks followed by additional treatment with ω-3 fatty acids (equivalent to 4 g eicosapentaenoic acid/docosahexaenoic acid daily) for 6 more weeks. With simvastatin treatment, the mean decreases in total cholesterol, low density lipoprotein (LDL) cholesterol, and apolipoprotein B (apo B) were 39%, 46%, and 36%, respectively. Only minor changes in high density lipoprotein (HDL) cholesterol and apo A-I were recorded. ω-3 fatty acids had minor additional effects. The most prominent effects on the blood coagulation system were the changes in extrinsic pathway inhibitor (EPI), which is the inhibitor of the factor VIIa–tissue thromboplastin complex. EPI activity decreased from a median of 153% to 111% (p < 0.001) with simvastatin treatment and to 112% (p<0.001) on the combined regimen. EPI activity was significantly correlated with LDL cholesterol (r=0.78), total cholesterol (r=0.77), apo B (r=0.65), and apo A-I (r=0.45). Multiple stepwise regression analysis showed that LDL cholesterol was the most important predictor of EPI activity, which suggests that a majority of EPI activity in plasma is associated with LDL. Moreover, the alteration in EPI activity was correlated closely with the corresponding alteration in LDL, which suggests a direct relation between a coagulation-inhibitor activity and a pharmaceutical lipid-related response. A small increase of median factor VII clotting activity, and of factor Vn clotting activity to factor VII antigen levels in patients receiving simvastatin alone was statistically significant but of questionable physiological significance. Platelet count, fibrinogen, protein C, heparin cofactor II, and plasminogen activator inhibitor were not significantly influenced by treatment. The clinical importance of the correlation between cholesterol levels and EPI activity remains unknown, but the changes may be relevant to thrombotic tendency. (Arteriosclerosis and Thrombosis 1991;11:138–145)

The importance of hyperlipidemia and thrombosis in the development of ischemic heart disease is well established. However, the precise relation between blood lipids and thrombosis is not yet known. One possibility is that prolonged hyperlipidemia may adversely affect the hemostatic system to cause a prethrombotic state.

Blood coagulation begins when factor VIIa binds to its membrane cofactor, tissue thromboplastin (tissue factor). The factor VIIa–tissue thromboplastin complex proteolytically activates factors IX and X. Several indications point to important effects of hyperlipidemia on the extrinsic coagulation system. Some studies have shown that a positive correlation of factor VII activity with triglyceride levels exists and that factor VII activity is amenable to dietary intervention. In normal arteries, tissue thromboplastin is delineated from the blood by the endothelium and tunica media. In diseased arteries, however, tissue thromboplastin is prevalent in the necrotic core of atherosclerotic plaques, and blood coagulation may then be triggered by a minor disruption of
the atherosclerotic plaque and exposure of tissue thromboplastin activity to the blood.

The factor VIIa—tissue thromboplastin complex is regulated by a serine protease inhibitor, which is called extrinsic pathway inhibitor (EPI), or lipoprotein-associated coagulation inhibitor.11,12 We had shown earlier that EPI activity in normal plasma may be separated into three different fractions by gel filtration. More than 90% of the activity was associated with higher molecular weights. Later experiments have shown that the two higher molecular weight fractions are due to association of EPI with the ratio of low density lipoproteins (LDLs) to very low density lipoproteins (VLDLs) and high density lipoproteins (HDLs), respectively (P.M. Sandset et al, unpublished observations, and Reference 13). More than 50% of the activity is probably associated with LDL.13,14

The nature and function of this EPI—lipoprotein association and the influence of hyperlipidemia on the expression of EPI activity is not known. In the present study, we explored the relation between serum lipids and several potentially important hemo-
static factors, including factor VII and EPI. The activity of two other coagulation inhibitors, protein C (which counters activated factors V and VIII) and heparin cofactor II (which counters thrombin), were also measured. An inhibitor of the fibrinolytic system, the fast-acting tissue plasminogen activator inhibitor (PAI-1), was also studied due to some evidence that this factor is correlated with triglyceride levels.15,16 Individuals with heterozygous familial hypercholes-
terolemia were selected because these individuals have increased LDL levels due to a relative defi-
ciency of LDL receptors and because lipid changes have shown that the two higher molecular weights are associated with higher molecular weights. Later experiments have shown that the two higher molecular weight fractions are due to association of EPI with the ratio of low density lipoproteins (LDLs) to very low density lipoproteins (VLDLs) and high density lipoproteins (HDLs), respectively (P.M. Sandset et al, unpublished observations, and Reference 13). More than 50% of the activity is probably associated with LDL.13,14

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ciency of LDL receptors and because lipid changes may be affected by treatment with 3-hydroxy-3-
methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors17 and ω-3 fatty acids (FAs).18 The main issues of the study were to determine the correlation of EPI activity with serum lipids and to determine whether EPI activity is amenable to therapeutic intervention to provide some clues as to what determines the levels of EPI activity in plasma.

Methods

Study Protocols and Blood Sampling

Eighteen otherwise-healthy men were admitted to the Lipid Clinic, Rikshospitalet, Oslo, Norway, because of heterozygous familial hypercholesterolemia. Mean age was 30 years (range, 18–48 years). The protocol consisted of 2–4 weeks of placebo medication followed by 14 weeks of simvastatin treatment (Merck Sharp & Dohme, Rahway, N.J.), 40 mg daily. Thirteen individuals consented to prolong the treatment with combined simvastatin (40 mg daily) and ω-3 FA concentrate (4 g daily) for 6 more weeks. The ω-3 FA preparation consisted of capsules of a highly purified fish oil concentrate (Eicomarine 60, Ny-
comed, Oslo, Norway) containing 280 mg eicosapentaenoic acid, 360 mg docosahexaenoic acid, and 60 mg docosapentaenoic acid. The diet (American Heart Association phase II diet) was kept constant throughout the study. Dietary intake was regularly surveyed by a dietician. Adverse effects to treatment were not observed. The protocol was approved by the ethical committee at Rikshospitalet, Oslo, Norway. Each individual was included in the trial after he gave his informed consent.

All blood samples were collected in tubes (Vacutainer, Becton Dickinson, Meylan Cedex, France) after a 12-hour overnight fast (between 8 and 10 AM). Blood for determination of serum lipoproteins and apolipo-
proteins (apos) was drawn every 4 weeks throughout the study period. Blood samples for coagulation analy-
sis were collected in triple-siliconated test tubes con-
taining 1:10 volume sodium citrate (0.129 M) at the end of the placebo period, at the end of the simvastatin period, and at the end of the combined simvastatin and ω-3 FA period. Plasma was immediately prepared by centrifugation (2,000g, 20 minutes, 20°C). Aliquots of plasma were stored within 2 hours in plastic tubes at −70°C until analysis. Platelet count was determined on an automatic cell counter.

Reagents

A crude preparation of human brain tissue thromboplastin was prepared essentially as described by Hjort19 by careful dissection of a human brain and removal of membranes and blood vessels, followed by extensive washing and homogenization of brain tis-
tue, extraction of homogenates with 45°C saline solution, and centrifugation at 2,000g for 20 minutes. Freeze-dried vials were stored at −70°C. The con-
tents were dissolved in distilled water to optimal concentration, at which the clotting time of normal plasma was 16 seconds (equal volumes of plasma, CaCl₂ [35 mM], and tissue thromboplastin). Rabbit brain tissue thromboplastin, Thromboplastin FS, was from Merz & Dade, Düdingen, Switzerland. Factor VII was purified as described by Rao and Bajaj.20 Lyophilized factor VII-deficient plasma from a pa-

tient with factor VII deficiency was kindly donated by Frank Brossad, Rikshospitalet, Oslo, Norway. Bo-
vine factor X and chromogenic substrate S-2222 were gifts from Kabi, Mölndal, Sweden. Reference plasma was pooled plasma from 25 healthy donors, aged 20–55 years. Bovine serum albumin (BSA), A-7030, was from Sigma Chemical Co., St. Louis, Mo. The Asserachrom VII Ag kit was from Stago, Asnières, France; Normotest was from Nycomed; and Coa-set PAI was from Kabi. Antisera against apo A-1 and apo B were from Behring Institut, Marburg, F.R.G.

Lipoproteins and Apolipoproteins

Total serum cholesterol and triglyceride concentra-
tions were determined on an automatic analyzer by conventional enzymatic methods with commercial reagents from Boehringer-Mannheim GmbH, Mann-
heim, F.R.G. HDL cholesterol was determined after precipitation of serum with antiserum against apo B. LDL cholesterol was calculated by the Friedewald formula:
LDL cholesterol = total cholesterol − HDL cholesterol − (triglyceride/2.2)21

Apo A-1 and apo B were determined after precipitation with antisera against apo A-1 and apo B, respectively.

Clotting Factor Assays

Factor VII clotting activity (factor VIIc) was determined with a standard clotting assay.22 Fifty microliters factor VII-deficient plasma, 100 µl human tissue thromboplastin (diluted 1:5), and 50 µl twice-barium-adsorbed bovine plasma were incubated for 3 minutes at 37°C. Fifty microliters test plasma (diluted 1:10 in 0.05 M Tris-HCl/0.1 M NaCl, pH 7.4) and 100 µl CaCl2 (35 mM) were then added, and the clotting times were recorded. Standard curves were established by dilutions of normal reference plasma.

Factor VII amidolytic activity (factor VIIa) was determined as described by Oswaldsson et al.23 by incubation of 25 µl test plasma (diluted 1:2,000, 1:4,000, and 1:8,000) with 75 µl of a combined reagent containing rabbit brain tissue thromboplastin (1:250), bovine factor X (0.25 units/ml), and CaCl2 (10 mM) for 30 minutes at 37°C. Fifty microliters S-2222 (2.7 mM) was then added for 10 minutes at 37°C, and the reaction was stopped by the addition of 25 µl citrate buffer (1 M). Dilutions were made in veronal buffer with 1% BSA, pH 7.4. Absorbance values at 405 nm were read against standard curves obtained by dilutions of reference plasma by the multiple parallel-line bioassay principle.

Factor VII antigen (factor VII:Ag) was determined with an enzyme-linked immunosorbent assay method (Asserachrom VII:Ag) according to the manufacturer. For all the factor VII assays, the activity or mass of 1 ml reference plasma was defined as 100%. All samples were assayed in duplicate and in random order.

Fibrinogen (determined by the method of Clauss24) and Normotest (performed as described by the manufacturer) were determined on fresh plasma. Normotest is a clotting assay that uses rabbit brain tissue thromboplastin and barium-adsorbed bovine plasma. Normotest is sensitive to factor VII.25

Coagulation Inhibitor Assays

EPI was determined with a three-stage, functional, chromogenic substrate method as described earlier.10,27 In the first incubation (250 µl), test plasma (heated at 56°C for 15 minutes to remove factor VII activity, diluted 1:250) was incubated with human factor VII (25 pM), bovine factor X (0.8 nM), and human brain tissue thromboplastin (diluted 1:100). Residual factor VIIa-tissue thromboplastin activity was determined by the addition of 50 µl bovine factor X (64 nM) in the second stage and 50 µl S-2222 (2.7 mM) in the third stage. The specificity of the assay was tested with anti-EPI antibodies (kindly donated by William Novotny, St. Louis, Mo.), which removed more than 95% of the EPI activity of normal plasma as determined in the assay. Reference values for EPI in an age-matched control population are 60–120% (±2 SD of the mean, n = 40).

Heparin cofactor II and protein C activities were determined in standard assays as described earlier.7,28 Standard curves for all the inhibitor assays were established by dilutions of reference plasma. Absorbance was read at 405 nm. The activity of 1 ml reference plasma was defined as 100% activity. PAI was determined with Coa-set PAI according to the manufacturer and expressed as arbitrary units (AU) per milliliter. All the inhibitor assays were performed in duplicate and in random order.

Statistics

The analyses were performed with the spss/pc+ v.2.0 statistical package (SPSS Inc., Chicago, Ill.). Median values and the 25th and 75th percentiles were calculated. Statistical comparisons between two groups were made by the paired Wilcoxon rank test. Correlations were tested by Pearson's coefficient of correlation. The independent associations of lipoproteins (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) and apoproteins (apo A-1 and apo B) on EPI activity levels were determined by stepwise multiple linear regression analysis in groups. A stepwise procedure was selected because of the exploratory nature of this analysis. Statistical significance was accepted when the probability of occurrence by chance was 1% or less (p ≤ 0.01).

Blood Lipids and Apolipoproteins

The results of treatment on blood lipid and apoprotein levels are shown in Table 1. Total serum cholesterol decreased 39% (p < 0.001) and 35% (p < 0.01) on simvastatin and combined simvastatin/ω-3 FA treatment, respectively. This decrease of total cholesterol was due to the effect on LDL cholesterol, which decreased 46% (p < 0.001) and 42% (p < 0.01), respectively. HDL cholesterol increased moderately: 15% (p < 0.01) and 12% (p < 0.05), respectively. Triglycerides decreased 22% (p < 0.05) on simvastatin but tended to increase on the combined regimen. The ratio of total cholesterol/HDL cholesterol was also highly significantly influenced by treatment but tended to increase on additional ω-3 FA.

Changes in lipoproteins were also reflected by similar changes in the apoproteins: Apo B decreased 42% on simvastatin and 36% on the combined regimen, whereas apo A-1 was only slightly affected.

Factor VII and Extrinsic Pathway Inhibitor

Factor VII activities and antigen levels were normal or even low before and during treatment (Table 2). The specific factor VIIc activity and Normotest (as an indirect measurement of factor VIIc activity) and the ratio of factor VIIc activity to factor VII:Ag level increased slightly but statistically significantly
TABLE 1. Serum Blood Lipids and Apolipoproteins in Patients With Familial Heterozygous Hypercholesterolemia Before and During Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=18)</th>
<th>Simvastatin (n=18)</th>
<th>Simvastatin + ω-3 fatty acids (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>9.45 (7.55–9.95)</td>
<td>5.40 (4.05–6.40)†</td>
<td>5.55 (4.68–6.33)†</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>7.40 (5.85–8.11)</td>
<td>3.75 (2.40–4.28)‡</td>
<td>3.78 (3.01–4.44)‡</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>0.95 (0.80–1.10)</td>
<td>1.00 (0.95–1.25)†</td>
<td>1.00 (0.93–1.15)*</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.12 (0.62–2.12)</td>
<td>0.76 (0.53–2.21)*</td>
<td>1.09 (0.78–1.91)</td>
</tr>
<tr>
<td>Total cholesterol/HDL cholesterol</td>
<td>8.81 (7.67–11.41)</td>
<td>4.77 (3.80–5.44)‡</td>
<td>5.87 (4.37–6.48)†</td>
</tr>
<tr>
<td>Apo A-I (mg/ml)</td>
<td>1.14 (1.07–1.31)</td>
<td>1.19 (1.12–1.16)</td>
<td>1.06 (1.00–1.17)†</td>
</tr>
<tr>
<td>Apo B (mg/ml)</td>
<td>2.17 (1.75–2.53)</td>
<td>1.26 (0.99–1.46)‡</td>
<td>1.39 (1.09–1.70)†</td>
</tr>
</tbody>
</table>

Placebo is equivalent to before treatment.

LDL, low density lipoprotein; HDL, high density lipoprotein; Apo, apolipoprotein.

Results are the median (25–75th percentiles).

* p<0.05, † p<0.01, ‡ p<0.001, paired Wilcoxon rank test (two-tailed) of the two patient groups (18 patients on simvastatin and 13 patients on combined simvastatin + ω-3 fatty acids) compared with the same number of patients before treatment.

Correlation of Extrinsic Pathway Inhibitor With Blood Lipids and Apolipoproteins

EPI activity was correlated with total cholesterol (r=0.77, p<0.001, Figure 1A), LDL cholesterol (r=0.78, p<0.001, Figure 1B), apo B (r=0.65, p<0.001, Figure 2B), and apo A-1 levels (r=0.47, p=0.001, Figure 2B), and with the ratio of total cholesterol to HDL cholesterol (r=0.40, p<0.005). EPI activity was not significantly correlated with HDL cholesterol (Figure 1C) or triglyceride levels (Figure 1D).

Stepwise multiple linear regression analysis of EPI activity on total cholesterol, LDL cholesterol, triglycerides, apo A-1, and apo B showed that LDL cholesterol (r=0.10.18, p<0.00001) and HDL cholesterol (r=4.23, p<0.0001) were the most significant predictors of EPI activity, accounting for 71% of the variance of EPI activity. Total cholesterol and apo B did not provide additional information when LDL cholesterol was present in the regression, but both total cholesterol and apo B would replace LDL cholesterol at nearly the same significance level when LDL was omitted from the regression. Similarly, apo A-1 did not provide additional information when HDL was present.

TABLE 2. Hemostatic Parameters in Patients With Familial Heterozygous Hypercholesterolemia Before and During Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=18)</th>
<th>Simvastatin (n=18)</th>
<th>Simvastatin + ω-3 fatty acids (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets (10^9/l)</td>
<td>2069 (225–293)</td>
<td>247 (211–271)</td>
<td>265 (246–307)</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>2.6 (2.2–3.1)</td>
<td>2.5 (2.3–2.7)</td>
<td>2.3 (1.9–2.5)</td>
</tr>
<tr>
<td>Normotest (%)</td>
<td>70 (65–85)</td>
<td>90 (85–104)†</td>
<td>90 (72–125)†</td>
</tr>
<tr>
<td>F VIIc (%)</td>
<td>88 (77–95)</td>
<td>93 (83–130)†</td>
<td>73 (63–84)*</td>
</tr>
<tr>
<td>F VIIam (%)</td>
<td>91 (87–114)</td>
<td>93 (82–125)</td>
<td>110 (90–140)</td>
</tr>
<tr>
<td>F VII:Ag (%)</td>
<td>80 (73–96)</td>
<td>75 (66–90)</td>
<td>83 (70–94)</td>
</tr>
<tr>
<td>EPI (%)</td>
<td>153 (131–180)</td>
<td>111 (96–138)‡</td>
<td>112 (98–120)‡</td>
</tr>
<tr>
<td>Protein C (%)</td>
<td>99 (88–111)</td>
<td>97 (75–103)</td>
<td>100 (84–111)</td>
</tr>
<tr>
<td>Heparin cofactor II (%)</td>
<td>87 (76–93)</td>
<td>92 (85–97)</td>
<td>82 (78–93)</td>
</tr>
<tr>
<td>PAI (AU/ml)</td>
<td>11.0 (8.4–18.9)</td>
<td>8.8 (7.0–14.1)</td>
<td>16.0 (9.0–26.0)</td>
</tr>
</tbody>
</table>

Placebo is equivalent to before treatment.

F, factor; C, clotting activity; am, amidolytic activity; Ag, antigen; EPI, extrinsic pathway inhibitor; PAI, plasminogen activator inhibitor; AU, arbitrary units.

Results are the median (25–75th percentiles).

* p<0.05, † p<0.01, ‡ p<0.001, paired Wilcoxon rank test (two-tailed) of the two patient groups (18 patients on simvastatin and 13 patients on combined simvastatin + ω-3 fatty acids) compared with the same number of patients before treatment.
in the regression, but apo A-1 would replace HDL cholesterol at nearly the same significance level when HDL cholesterol was omitted from the equation.

To demonstrate the determinants for the changes in EPI activity, the relative values of EPI activity before and during treatment were calculated and plotted against the relative values of blood lipids and apoproteins. The linear regression for each comparison was calculated. This analysis revealed that the relative change of EPI activity was correlated with the relative changes of LDL cholesterol ($r=0.55, p<0.01$, Figure 3), total cholesterol ($r=0.48, p<0.01$), and apo B ($r=0.52, p<0.01$). However, the relative decreases of LDL cholesterol, total cholesterol, and apo B were greater than the decrease in EPI activity (Figure 3). The multiple stepwise linear regression analysis of the relative change of EPI activity on the relative change in blood lipids and apoproteins revealed that LDL cholesterol ($t=3.50, p<0.01$) was the only significant predictor for the change of EPI activity. In this analysis, both apo B and total cholesterol would replace LDL cholesterol when LDL cholesterol was omitted from the regression. This result, therefore, suggests a direct relation between EPI activity and the lipid-related response.

**Effect of Treatment on Other Hemostatic Parameters**

Blood platelet count, fibrinogen, heparin cofactor II, and PAI-1 were not significantly influenced by

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**Figure 1.** Scatterplots showing correlation between extrinsic pathway inhibitor (EPI; %) activity and (panel A) total cholesterol, (panel B) low density lipoprotein (LDL) cholesterol, (panel C) high density lipoprotein (HDL) cholesterol, and (panel D) triglycerides. Cholesterol and triglyceride measurements are in mmol/L. ○ Placebo; ● simvastatin; □ simvastatin + ω-3 fatty acids.

**Figure 2.** Scatterplots showing correlation between extrinsic pathway inhibitor (EPI; %) activity and (panel A) apolipoprotein A-1 and (panel B) apolipoprotein B levels (both in g/l). ○ Placebo; ● simvastatin; □ simvastatin + ω-3 fatty acids.
of EPI activity was significantly correlated with the relative decrease in LDL cholesterol (and total cholesterol and apo B). The multivariate analysis showed that this decrease in EPI activity, to a large extent, was predicted by changes in LDL (accounting for 78% of the variance of EPI activity). The present results, therefore, strongly suggest a direct relation between EPI activity and the pharmaceutical lipid-related response. The nature of these changes in EPI activity may be due to real changes of the EPI mass or to altered activity of EPI induced by the association with lipoproteins.

The extrinsic coagulation system may play an important role in the initiation of blood coagulation in atherosclerotic disease. As has been elegantly shown, tissue thromboplastin is prevalent in the necrotic core of atherosclerotic plaques. Possibly, intermittent exposure of tissue thromboplastin at the surface of an atherosclerotic plaque may cause continuous low-grade triggering of blood coagulation. One study has also shown that factor VIIc activity is independently associated with the risk for subsequent development of ischemic heart disease in middle-aged men. It is tempting to speculate that the increase of EPI activity levels in individuals with hypercholesterolemia may be a compensatory mechanism to prevent activation of the blood coagulation system by factor VII and tissue thromboplastin. It is notable that hyperlipidemic patients often have advanced vessel-wall changes without thromboembolic events. Rather, thrombosis occurs as the end stage of the atherosclerotic disease in greatly narrowed and atheromatous segments of the blood vessels. Reduced blood flow probably plays the dominant role in the development of thrombosis in such vessels.

In this study, factor VII activity and antigen levels were normal or even low and remained within the normal range during treatment. A small increase of factor VIIc activity and of factor VIIc activity/factor VII:Ag level was recorded during simvastatin treatment alone, which indicates some activation of factor VII. The mechanism of this increase of factor VII activity on simvastatin alone is not clear and cannot be explained by triglyceride-rich lipoproteins since triglycerides actually decreased while the patients were on simvastatin. Unless extensive coronary atherosclerosis is present with a severely compromised coronary circulation, the small increase of factor VII activity caused by simvastatin is not likely to be of major clinical significance. The additional effect of ω-3 FAs (Table 2) to reduce factor VIIc activity in this study may be a potentially important beneficial effect of ω-3 FAs. However, except for one recent study, other studies have failed to show any effect of fish oil consumption on factor VIIc activity.

We have seen earlier that clinical situations associated with increased factor VIIc activity, that is, ischemic heart disease and pregnancy, are also associated with increased EPI activity, which suggested balanced changes of activator (factor VII) and inhibitor (EPI). This study, however, shows that
factor VII activity and EPI activity may be differentially altered by blood lipids. As yet, the physiological meaning of the factor VII/EPI ratio is not clear, but one possibility is that altered factor VII/EPI ratio may cause a prothrombotic state.

There have been a few reports of bleeding, increased prothrombin time, or both in patients simultaneously taking an HMG-CoA reductase inhibitor and warfarin. In this study, neither fibrinogen, heparin cofactor II, protein C, PAL-1, nor blood platelets were affected. Altogether, these changes do not predict bleeding diathesis.

The lipid-lowering effect of simvastatin in this study was similar to that observed in earlier studies (for a review, see Reference 17). The addition of ω-3 FAs had only minor additional effects, with a tendency to increased triglyceride concentration, the ratio of total cholesterol/HDL cholesterol, and apo B (Table 1). Most human feeding trials with fish oil concentrates have shown a decrease of triglycerides, but these patients may not be directly comparable to the present population, in whom ω-3 FAs were an additional treatment to simvastatin. Whether these changes in the lipid parameters are of clinical significance remains to be investigated.

Acknowledgments

The excellent technical assistance of Mette Lie Larsen and Lise-Mette Aamodt is greatly appreciated. We are grateful to Samuel I. Rapaport for helpful comments during preparation of this manuscript. We acknowledge Merck Sharp & Dohme, Norway, for supplies of simvastatin and Nycomed, Norway, for supplies of Eicomarine.

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receiving either oral anticoagulants or matching placebo. Thromb Res 1989;53:467–474

KEY WORDS • coagulation inhibitors • extrinsic pathway inhibitor • factor VII • plasminogen activator inhibitor • familial hypercholesterolemia • HMG-CoA reductase inhibitor • simvastatin • apolipoproteins • lipoproteins
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doi: 10.1161/01.ATV.11.1.138

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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