Endothelial protein C receptor (EPCR) plays an important role in the inhibition of thrombin generation by its participation in the PC pathway. As an integral endothelial membrane protein it captures circulating PC and presents it to an adjacent thrombin-thrombomodulin complex which activates the PC with a consequent inhibition of coagulation factors Va and VIIIa, resulting in reduced thrombin generation. We and others have previously reported altered functional characteristics associated with an amino acid change within the membrane spanning region of EPCR (Ser219Gly), both by in vitro analysis and in data derived from ex vivo plasma samples. Increased thrombin generation, as determined by prothrombin F1+2 (F1+2) levels, was found in those with the EPCR 219Gly allele in a large study of patients with type 2 diabetes and in healthy individuals within the large prospective study of heart disease, Northwick Park Health Study II (NPHSII). A large difference in soluble EPCR levels across EPCR Ser219Gly genotype groups is now well established both in health and disease, with at least 70% of the variance of soluble EPCR levels in plasma being caused by the EPCR Ser219Gly variant. In vitro analysis has confirmed increased shedding of EPCR in those with the Gly allele.

Objective—The purpose of this study was to determine the effect of a variant in EPCR (Ser219Gly), previously shown to affect EPCR shedding, on plasma FVII, FVIIa, and downstream markers of activated coagulation.

Methods and Results—Statistical analysis was undertaken in ≈2000 healthy middle aged men (NPHSII). Higher soluble EPCR levels were confirmed for Gly allele carriers (P<0.0001). Significantly higher levels of FVII, FVIIa, and downstream markers of activated coagulation in the extrinsic pathway (FIX activation pep [FIXpep]; FX activation pep [FXpep]), and prothrombin F1+2 (F1+2) were identified in baseline samples, in Gly carriers compared to Ser/Ser (P<0.04 for trend). In repeat samples collected for up to 5 years, levels of FVII and F1+2 were higher in Gly allele carriers compared to Ser/Ser by (FVII: 6.9% CI 5.5 to 8.4 in Ser/Gly; and 23.4% CI 16.3 to 30.8 in Gly/Gly, P<0.0001), (F1+2: 8.1% CI 5.2 to 11.1 in Ser/Gly; 25.2% CI 11.8 to 40.3 in Gly/Gly, P<0.04), confirming reproducibility of findings at baseline. Molar ratios for FIXpep, FXpep, and F1+2 to FVIIa were constant in Ser/Ser and Ser/Gly but tended to be higher in Gly/Gly, reaching statistical significance for FIXpep:FVIIa (P=0.04).

Conclusions—These data suggest that higher levels of FVII and FVIIa circulate when EPCR shedding is greatest. Furthermore, these results suggest consequences for activation of extrinsic coagulation. (Arterioscler Thromb Vasc Biol. 2009;29:1968-1974.)

Key Words: endothelial protein C receptor ■ FVIIa ■ extrinsic coagulation ■ FIX activation peptide ■ FX activation peptide ■ prothrombin F1+2

See accompanying article on page 1712

Recent in vitro analysis by surface plasmon resonance of FVIIa passed over soluble EPCR bound to the surface, and cell surface EPCR binding to both FVII and FVIIa has suggested that EPCR also acts as a cellular receptor for activated factor VII (FVIIa) and FVII on endothelium. FVIIa and FVII bound to EPCR with a similar affinity compared to binding of PC and activated PC to EPCR. Furthermore, FVIIa that had bound to EPCR was unable to accelerate either FVIIa activation of FX or to activate protease activated receptors. FVIIa endocytosis was also facilitated by its binding to EPCR. EPCR binding is therefore suggested as a clearance mechanism for FVIIa. An in vitro study has also shown that blocking the FVII binding site of EPCR on the endothelial surface increased the generation of FXa by FVIIa,
Further suggesting a physiological hemostatic consequence of EPCR-FVIIa binding. Soluble EPCR was shown to dose-dependently inhibit the activation of FX by the FVIIa-tissue factor (TF) complex. These findings suggest, in terms of the FVII/FVIIa binding, that higher levels of endothelial or soluble EPCR may shift hemostatic balance toward anticoagulant activity, although it is difficult to predict the relative effects of these processes in vivo.

Within NPHSII, markers of coagulation activity have been measured at several steps along the extrinsic or tissue factor pathway. A sensitive assay to the peptide liberated (FIXpep) with the generation of activated factor IX (FIXa) has demonstrated that FIXa generation in vivo results mainly from activity of the tissue factor pathway, rather than the contact or intrinsic pathway (factor XII, prekallikrein, high-molecular-weight kininogen, factor XI). Levels of FIXpep were shown to be reduced in hereditary FVII or FIX deficiency. Similarly, levels of FXpep were shown to be lower in patients with FVII deficiency.

In a recent study of NPHSII, a higher ratio of FIXpep: FVIIa was found to be an independent risk for heart disease and was as good as or better than the classic and inflammatory risk factors used in risk algorithms. In the current analysis of this large study of middle-aged men, healthy at the time of sampling, measurements of FVII and FVIIa have been assessed by EPCR Ser219Gly genotype, and the consequences of this on activation of coagulation has been studied using activation markers within the extrinsic coagulation pathway (FIXpep and FXpep). Measurements of activated factor XII (FXIIa) and F1+2 were used also to determine any effect on coagulation outside the extrinsic pathway, and thrombin generation, respectively.

Methods

Study Cohort

NPHSII is a prospective study of heart disease currently with 15 years follow-up. The study involved 2997 men who gave written informed consent, and was approved by the institutional ethics committee. Subjects did not fast before blood collection but were instructed to avoid heavy meals. They were also requested not to smoke or to take vigorous exercise from midnight before sampling.

EPCR Genotyping

EPCR genotyping was determined using PCR, followed by restriction digest, and visualized using microarray diagonal gel electrophoresis, as reported previously.

Measurements of Coagulation Factors and Markers of Activated Coagulation

For the current analysis, only samples without a questionable venepuncture performance were included, following a scoring system by predetermined criteria. FVII levels were measured by coagulant (FVIIc) and antigen (FVIIa) levels. Markers of an activated extrinsic pathway (FIXpep, FXpep, and FIXpep,11 FVIIa), and a coagulation marker outside the extrinsic coagulation pathway (FXIIa, Axis-Shield) together with a marker of thrombin generation (F1+2) were measured as described previously, in baseline samples. Numbers for those with genotype data corresponding to EPCR Ser219Gly and each coagulation marker, in baseline samples are as follows: FVIIc (n = 2427), FVIIag (n = 2273), FVIIa (n = 1086), FIXpep (n = 1259), FXpep (n = 1120), FXIIa (n = 1970), F1+2 (n = 2188).

In addition, FVIIc levels had been measured in samples collected at 1, 2, 3, 4, and 5 years and F1+2 levels had been measured at 1,

Results

Levels of FVIIc, FVIIag, and FVIIa in Baseline Samples by EPCR Ser219Gly Variant

All 3 measurements showed a statistically significant increasing trend from lowest levels in Ser/Ser to higher levels in Ser/Gly with the highest levels in those who were Gly/Gly (P < 0.04, Figure 1). Similarly, for all 3 measurements, levels were significantly higher in a combined group with at least 1 Gly allele compared to those with only Ser alleles (P < 0.04, Figure 1). The significances of the associations with EPCR Ser219Gly after adjustment for confounders (center, age, smoking, creatinine, CRP) were: P < 0.0001 for FVIIc; P < 0.0001 for FVIIag; P = 0.05 for FVIIa, confirming the significance of each association.

Markers of Activated Coagulation Downstream From FVIIa, in Baseline Samples, by EPCR Ser219Gly Variant

To determine whether an increase in circulating FVII and FVIIa could have consequences for downstream events in the extrinsic coagulation pathway, FIXpep, FXpep, and thrombin generation (F1+2) were analyzed. Both FXpep (P = 0.04) and FIXpep (P = 0.01) were elevated in those who were heterozygous and homozygous for EPCR Ser219Gly compared to non-carriers and showed a statistically significant trend (P < 0.04, Figure 2). FXIIa however, a coagulation marker outside the extrinsic system, showed no significant difference in levels by variant group (P > 0.73, Figure 2). The previously reported significantly higher F1+2 levels by EPCR genotype
in these healthy middle-aged men are included here also for completeness. F1+2 levels were significantly higher in the EPCR 219Gly carrier groups (P=0.001) and by trend (P=0.0001, Figure 2). These results show slightly different geometric mean levels to those in the previous publication because of removal, in the current study, of those individuals whose blood sampling was thought to be of inadequate quality. This did not, however, change the statistical significance of the results. The significance of the associations with EPCR variant site after adjustment for potential confounders,
Although levels were considerably higher in those who were Ser/Ser (Figure 3). However, although numbers were small, there was a tendency toward higher molar ratios in those who were Gly/Gly, which reached statistical significance for the ratio of FIXpep:FVIIa (1.8-fold higher than in noncarriers, P=0.0005). After adjustment for the differences between years, levels of FVIIc in Ser/Gly were 6.9% (95% CI: 5.5 to 8.4) higher than in Ser/Ser and in Gly/Gly were 23.4% (95% CI: 16.3 to 30.8) higher (Table 1A). Similarly after adjustment F1+2 levels were 8.1% (95% CI: 5.2 to 11.1) higher in Ser/Gly than in Ser/Ser and 25.2% (95% CI: 11.8 to 40.3) higher in Gly/Gly (Table 1B).

**Molar Ratios of Coagulation Activation Markers, in Baseline Samples, by EPCR Ser219Gly Variant**
In line with the other coagulation activation markers, which were reported as molar concentrations, FVIIa was converted to a molar concentration using a molecular weight estimation of 51.6 kDaltons. Molar ratios for FIXpep:FVIIa, FIXpep:FVIIa, and F1+2:FVIIa were calculated to determine whether they differed by EPCR variant. Although levels of the 3 extrinsic pathway activation markers (FVIIa, FIXpep, and FXpep) and a marker of thrombin generation (F1+2) were higher in carriers of the Gly allele, molar ratios for these 3 activation markers to FVIIa levels were constant in Ser/Ser and Ser/Gly (Figure 3). However, although numbers were small, there was a tendency toward higher molar ratios in those who were Gly/Gly, which reached statistical significance for the ratio of FIXpep:FVIIa (1.8-fold higher than in noncarriers, P=0.04), and >1.3-fold higher than in noncarriers for the other 2 ratios (P=0.20 for F1+2:FVIIa; P=0.10 for FXpep:FVIIa).

### Table 1A. FVIIc levels in baseline samples and years 1–5 after recruitment in those who were EPCR219 Ser/Ser, Ser/Gly, and Gly/Gly

<table>
<thead>
<tr>
<th>EPCR Genotype</th>
<th>Baseline FVIIc %</th>
<th>Year 1 FVIIc %</th>
<th>Year 2 FVIIc %</th>
<th>Year 3 FVIIc %</th>
<th>Year 4 FVIIc %</th>
<th>Year 5 FVIIc %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ser/Ser n=1298</td>
<td>103.3 (27.0)</td>
<td>106.8 (27.0)</td>
<td>108.6 (27.8)</td>
<td>108.5 (27.0)</td>
<td>121.0 (33.5)</td>
<td>122.0 (33.8)</td>
</tr>
<tr>
<td>Ser/Gly n=253</td>
<td>109.2 (28.9)</td>
<td>113.5 (30.4)</td>
<td>115.8 (31.7)</td>
<td>116.9 (29.1)</td>
<td>131.2 (35.3)</td>
<td>130.2 (34.7)</td>
</tr>
<tr>
<td>Gly/Gly n=13</td>
<td>142.0 (28.0)</td>
<td>137.9 (30.7)</td>
<td>122.0 (28.2)</td>
<td>122.3 (35.5)</td>
<td>155.3 (30.0)</td>
<td>149.4 (28.8)</td>
</tr>
</tbody>
</table>

*P* value: <0.0001 for FVIIc, 0.0001 for F1+2 levels from baseline to year 5, by EPCR Ser219Gly variant.

### Table 1B. Prothombin F1+2 levels in baseline samples and years 1–4 after recruitment in those who were Ser/Ser, Ser/Gly, and Gly/Gly

<table>
<thead>
<tr>
<th>EPCR Genotype</th>
<th>Baseline F1+2 μmol/L</th>
<th>Year 1 F1+2 μmol/L</th>
<th>Year 2 F1+2 μmol/L</th>
<th>Year 3 F1+2 μmol/L</th>
<th>Year 4 F1+2 μmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ser/Ser n=961</td>
<td>0.68 (0.27)</td>
<td>0.68 (0.26)</td>
<td>0.69 (0.27)</td>
<td>0.69 (0.26)</td>
<td>0.72 (0.28)</td>
</tr>
<tr>
<td>Ser/Gly n=177</td>
<td>0.75 (0.29)</td>
<td>0.72 (0.29)</td>
<td>0.76 (0.30)</td>
<td>0.73 (0.27)</td>
<td>0.79 (0.33)</td>
</tr>
<tr>
<td>Gly/Gly n=9</td>
<td>0.95 (0.29)</td>
<td>0.86 (0.28)</td>
<td>0.80 (0.36)</td>
<td>0.94 (0.61)</td>
<td>0.81 (0.32)</td>
</tr>
</tbody>
</table>

*P* value: <0.0001 for F1+2 levels in baseline to year 5, by EPCR Ser219Gly variant.

### Table 1C. sEPCR levels in baseline (or year 1), year 2, and year 5 after recruitment in those who were EPCR219 Ser/Ser, Ser/Gly, and Gly/Gly

<table>
<thead>
<tr>
<th>EPCR Genotype</th>
<th>Baseline or Year 1 sEPCR ng/ml</th>
<th>Year 2 sEPCR ng/ml</th>
<th>Year 5 sEPCR ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ser/Ser n=54</td>
<td>82.6 (34.6)</td>
<td>94.9 (30.5)</td>
<td>90.8 (35.7)</td>
</tr>
<tr>
<td>Ser/Gly n=34</td>
<td>212.4 (87.6)</td>
<td>237.6 (116.2)</td>
<td>225.4 (93.1)</td>
</tr>
<tr>
<td>Gly/Gly n=11</td>
<td>270.5 (233.0)</td>
<td>328.2 (283.9)</td>
<td>319.5 (263.1)</td>
</tr>
</tbody>
</table>

*P* value: <0.0001 for sEPCR levels in baseline to year 5, by EPCR Ser219Gly variant.
Levels of sEPCR Across Ser219Gly Genotype
To confirm previous results that sEPCR levels differ by Ser219Gly genotype, baseline (or year 1) samples were assessed across the genotype groups. No significant difference could be found between the samples at baseline (n=84) and year 1 (n=15, _P_=0.52), and accordingly, these were assessed as 1 group. Significantly higher levels were identified for those with the Gly allele, as expected (_P_<0.0001, both unadjusted and adjusted for those who later had a CHD event). Geometric mean levels in Ser/Ser were 82.6 (SD 34.6, n=99; year 2, 99.3 [102.4] n=90, _P_=0.08), in Ser/Gly were 212.4 (SD 87.6, n=34) and in Gly/Gly were 270.5 (SD 233.0, n=53, _P_=0.01) compared to baseline (or year 1), both within genotype groups (Table 1). sEPCR levels were significantly higher in year 2 and in year 5 samples compared to baseline (or year 1), both within genotype groups (Table 1) and overall (geometric mean [SD]: baseline or year 1, 130.3 [90.8] n=99; year 2, 149.3 [102.4] n=99; year 5, 142.7 [97.6] n=99; _P_<0.0001). sEPCR levels were analyzed across all genotype groups by correlation with FVII levels and with the coagulation activation markers in baseline or (year 1) samples. Significant positive correlations were identified with FVII levels (FVIIc _r_=0.64, _P_=0.003) and with prothrombin F1+2 levels (_r_=0.27, _P_=0.04), but not with FXIIa (_r_=-0.03, _n_=88, _P_=0.78). The correlation between FVIIc and sEPCR levels appeared higher within Ser/Gly (FVIIc _r_=0.42, _n_=34, _P_=0.01) compared to Ser/Ser, which showed no significant correlation (_r_=0.11, _n_=53, _P_=0.42) and even higher in Gly/Gly (_r_=0.64, _n_=11, _P_=0.03), although numbers were small in this group. Correlations between the extrinsic pathway activation markers and sEPCR were not significantly correlated in Ser/Ser, but became significantly correlated in Ser/Gly for FVIIa (_r_=0.64, _P_=0.001, _n_=23) and FIX pep (_r_=0.54, _P_=0.01, _n_=21). Insufficient paired measurements were available for correlation analysis of FVIIa, FIXpep, and FX pep in Gly/Gly. F1+2 levels only became borderline significantly correlated with sEPCR within Gly/Gly (_r_=0.61, _n_=9, _P_=0.08), although numbers were small.

Discussion
Previous studies have shown a large difference in soluble EPCR levels across EPCR Ser219Gly variant groups, being 2-fold higher in Ser/Gly and 4-fold higher in Gly/Gly compared to noncarriers of Gly.2-4,6 The current analysis has confirmed the higher levels of sEPCR identified for the Gly allele. The large variability in levels for the “Gly” allele, which can be seen in the current study by the large SD for the Gly allele, has been suggested to be caused at least in part by alternative splicing of the mRNA for this allele, resulting in a longer protein that is expressed, but which does not associate with the membrane. A minor portion of plasma sEPCR has been identified as this alternatively spliced variant in carriers of the Gly allele.18 It has been suggested that the plasma level of the alternatively spliced variant may be related to inflammatory processes.18 The levels of sEPCR in the current study were measured in health and, as the alternatively spliced variant would be expected to be present in only minor amounts, would not be expected to account for the findings in the current study.

The current data would support the concept that reduced amounts of EPCR on the surface of endothelium, attributable to increased shedding, in EPCR Gly carriers, has a consequence for reduced binding of FVII and FVIIa, resulting in...
higher circulating levels of these coagulation pathway proteins. These findings extend those reported for binding of FVII and FVIIa to surface expressed EPCR by in vitro analysis,7,8,9 and suggest that binding of FVII and FVIIa may have physiological significance. Analysis of FVIIc levels over 5 years in a large number of samples confirmed the effect of the EPCR variant site on levels and gives strong evidence for the reproducibility of the results.

The finding of higher levels of downstream activation markers for the extrinsic pathway (FIXpep, FXpep) but not for a coagulation marker outside of the extrinsic pathway (FXIIa) suggests that the reduced binding of FVIIa in those with the Gly allele may have consequences for activation of these coagulant proteins, resulting in an increase in thrombin generation (F1 +2). Again, as for FVIIc levels over 5 years, the consistent effect of the variant site on F1 +2 levels over 4 years gives strong evidence for the reproducibility of these results.

The question arises as to whether the increased activation through the extrinsic pathway is directly related to the lower FVII and FVIIa binding to the endothelial cell surface or via another mechanism. In this regard, it may be expected that reduced amounts of EPCR on the surface of endothelium would impact on PC binding also, leading to reduced activated PC generation in Gly carriers. The consequence of this would be reduced inhibition of the thrombin feedback loop leading potentially to an increase in FIXpep, FXpep, and F1 +2 levels. FVIIa levels, however, would not be expected to increase in this case, as it has been suggested that thrombin is probably not a physiologically important activator of FVII in vivo.19 To disentangle the potential consequences of increased FVIIa level per se on downstream activation of the extrinsic coagulation system, compared to the consequences of reduced amounts of activated PC generation, a molar ratio of each downstream activated coagulation marker to FVIIa was calculated.

Although the increase in FVIIa levels in Ser/Gly was statistically significant compared to Ser/Ser, the percentage increase was small. For this small increase in FVIIa level in heterozygotes, the molar ratio of each activation marker in the extrinsic coagulation system to FVIIa was constant, compared to each ratio in Ser/Ser, suggesting that the higher FVIIa level in carriers of one Gly allele leads to an equally high “knock-on” effect of downstream activation.

The tendency toward an increased molar ratio for FIXpep: FVIIa (1.8-fold), FXpep:FVIIa (1.6-fold), and F1 +2:FVIIa (1.3-fold) in those heterozygous for Gly, however, does suggest that further deregulation of activated coagulation downstream from FVIIa is likely in those with the highest levels of EPCR shedding. Tissue factor pathway inhibitor (TFPI) is the most important regulator of the FVIIa-tissue factor complex, but differences in levels of TFPI would not be expected to differ by EPCR variant and account for these results. The altered ratio may represent the added effect of a deregulated PC pathway, with reduced inhibition of the thrombin feedback loop, but requires further study. Collectively, the findings suggest 2 physiological roles for endothelial EPCR in the regulation of thrombin generation: binding and clearance of FVIIa, in addition to regulation of the thrombin feedback loop.

In vitro analysis has suggested that FVII and FVIIa will bind soluble EPCR in addition to endothelial-bound EPCR and that soluble EPCR-bound FVIIa has reduced ability to activate FX.9 The higher soluble EPCR levels associated with the Gly allele, therefore, may be expected to compensate for the reduced endothelial located EPCR, but it is not clear what the importance of this mechanism would be in vivo. This finding is in contrast to activated PC binding to soluble EPCR, which unlike membrane-bound EPCR has been suggested to inhibit the functional activity of activated PC, rather than promote it.20 In mice, it has been suggested that only supraphysiologic levels of soluble EPCR could influence PC activation and exaggerate the coagulant response.21 This is a complicated dynamic physiological process, therefore, and it is difficult to predict what would actually happen in vivo, from in vitro studies. The current study has not addressed the relative contribution of the endothelial versus circulating levels of soluble EPCR to bind FVII and FVIIa, nor the relative effects of the membrane versus circulating compartments of EPCR-FVIIa complex on downstream hemostasis. However, the results have suggested that in health, when EPCR shedding is high (Gly/Gly), the balance of these processes leads to relatively higher downstream activation of extrinsic coagulation, determined by molar ratios of the downstream activation markers to FVIIa, than was observed for the other 2 genotype groups. At an intermediate level of EPCR shedding (Ser/Gly), whereas increased FVIIa levels paralleled an increased activation of extrinsic coagulation, the relative amounts of FVIIa and downstream activation markers were constant (determined by molar ratios), compared to those who have the lowest level of EPCR shedding.

These findings, in Ser/Ser compared to Gly/Gly, help the understanding of the 3-fold elevation in risk for heart disease for Gly/Gly identified previously in NPHSII2 and extend the findings for the association of a higher FIXpep:FVIIa in those with heart disease without reference to genotype in NPHSII also.12 The small increase in extrinsic coagulation markers measured in health in heterozygotes for Gly in the current study does not detrimentally affect clinical outcome for heart disease.2 In these heterozygotes, the molar ratio of FIXpep: FVIIa did not increase above that seen for Ser/Ser and further suggests the usefulness of this molar ratio in prediction of risk for heart disease.

As stated previously, analysis of NPHSII has shown a higher molar ratio for FIXpep:FVIIa in baseline samples in those who went on to have a heart disease event.12 This ratio was attributable to both higher FIXpep levels and lower FVIIa levels in those who later developed a heart disease event. The potential explanation for these results was through increased amounts of intravascular tissue factor, with the lower FVIIa levels suggested to arise because of binding of FVIIa to tissue factor and loss of circulating measureable FVIIa. In contrast, although the current analysis would suggest that homozygotes for EPCR 219Gly are hemostatically compromised by an increased FIXpep:FVIIa molar ratio and were previously associated with heart disease in NPHSII,2 we have shown FVIIa levels to be higher in Gly/Gly. So these
results indicate 2 situations associated with risk for development of heart disease, in healthy individuals: High FIIxpep, low FVIIa, high FIXxpep:FVIIa ratio across all individuals in NPHSII; and high FIXxpep, high FVIIa, high FIXxpep:FVIIa ratio in EPCR 219Gly homozygotes.

In summary, we have extended previous in vitro analysis which showed that FVII and FVIIa bind endothelial and sEPCR, by providing evidence that a functional variant site in EPCR has consequences both for plasma levels of FVIIa and for downstream activation of the extrinsic coagulation pathway. The stability of these results across 4 to 5 years, shown for FVIIc and F1+2 levels in this very large study, provides strong evidence for the variant effect. These results have also extended a previous study of NPHSII, suggesting that an increased ratio of FIXxpep:FVIIa is associated with future development of heart disease. The consequences of the findings for the EPCR variant site for heart disease and other conditions associated with increased inflammatory or thrombotic processes, require further study.

Limitations of the Study

The ability to measure activated PC in this study would have been useful but is not possible as samples require collection into a specific anticoagulant cocktail.

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Disclosures

J.H.M. has royalty income from patents related to assays used in this work; M.P.E. licensed the technology for the FXIIa assay to Axis-Shield. J.H.M. has royalty income from patents related to assays used in this work; M.P.E. licensed the technology for the FXIIa assay to Axis-Shield.

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FVII, FVIIa, and Downstream Markers of Extrinsic Pathway Activation Differ by EPCR Ser219Gly Variant in Healthy Men
Helen A. Ireland, Jackie A. Cooper, Fotios Drenos, Jayshree Acharya, Jacqueline P. Mitchell, Ken A. Bauer, James H. Morrissey, M. Peter Esnouf and Stephen E. Humphries

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