The complex of activated protein C and Protein C inhibitor (APC-PCI) in diabetics treated with atorvastatin.

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Background
In steady state, the complex of activated protein C and Protein C inhibitor (APC-PCI) is considered to reflect the formation of activated protein C.

We studied whether or not APC-PCI is related to diabetic or inflammation markers of the liver and endothelium and to fibrinolysis variables.

In addition the effect of atorvastatin treatment was studied.

Methods
A total of 24 type II diabetics (m/v 50/50) without manifest cardiovascular disease, mean age 59 y, mean BMI 31 were studied (DALI-study'). APC-PCI was measured by EIA (Biporto Diagnostics, Sweden).

Results

a) Baseline metabolic correlations for APC-PCI
APC-PCI is normally distributed: Mean (SD) 0.63 ±0.16 (SD) μg/ml.
No correlation with:
- age and gender ($\sigma^2<6\%$)
- lipids (LDL; HDL; TG; FFA; apoA, B; $\sigma^2<6\%$)
- HbA1c, glucose, BMI ($\sigma^2<2\%$)
- endothelial markers: s-VCAM, s-selectin, vWF, t-PA ($\sigma^2<1\%$)

Negative correlation with fibrinogen:

![Figure 1: pre-treatment fibrinogen vs APC-PCI](image)

Figure 1: pre-treatment fibrinogen vs APC-PCI ($\sigma^2=24\%; p=0.021$).
The negative correlation with fibrinogen is supported by negative trends for IL-6 and SAA ($\sigma^2>10\%$).

b) Atorvastatin effect on APC-PCI and s-TM

Figure 2A,B: % Changes in APC-PCI (A) and s-TM (B) for 3 dose groups: placebo, 10 and 80 mg atorvastatin

Six month placebo, 10 or 80 mg atorvastatin resulted in median changes in APC-PCI of $+3\%$; $-9\%$ (n.s) and $-12\%$ ($p=0.012$, Wilcoxon signed ranks test), resp.

s-TM changed: $-4.05\%$ ; $+2.3\%$ ($p=0.01$) and $+5.2\%$ ($p=0.002$).

c) Further haemostatic changes.

Figure 3A,B. Associations between changes in s-TM, APC-PCI, d-dimer $^1$, and PAI-1 $^1$ analysed by association (figA: $\sigma^2$) and factor analysis (fig B).

The data in figure 3 indicate that associations between changes follow two mechanisms.

Discussion
Figure 3 suggests that the changes follow the model:

$s-$TM $^*$ ↑; APC-PCI ↓ ; F 1+2 2 ↓ + D-dimer ↓

(*) high s-TM is anticoagulant $^3$

This collectively indicates reduced thrombin formation.

Conclusions
- The Rx induced APC-PCI lowering signals decreased thrombin formation. Increase in s-TM is the suggested mechanism.
- By another mechanism fibrinolysis is enhanced.
It is suggested that reduced coagulation and increased fibrinolysis collectively associate with the reduced venous thrombosis rate under statin treatment.

References
1) Van de Ree et al. JTH 1(2003) 1753