# Factor VIIa-Antithrombin complex levels and Factor Xa generation in CAD patients

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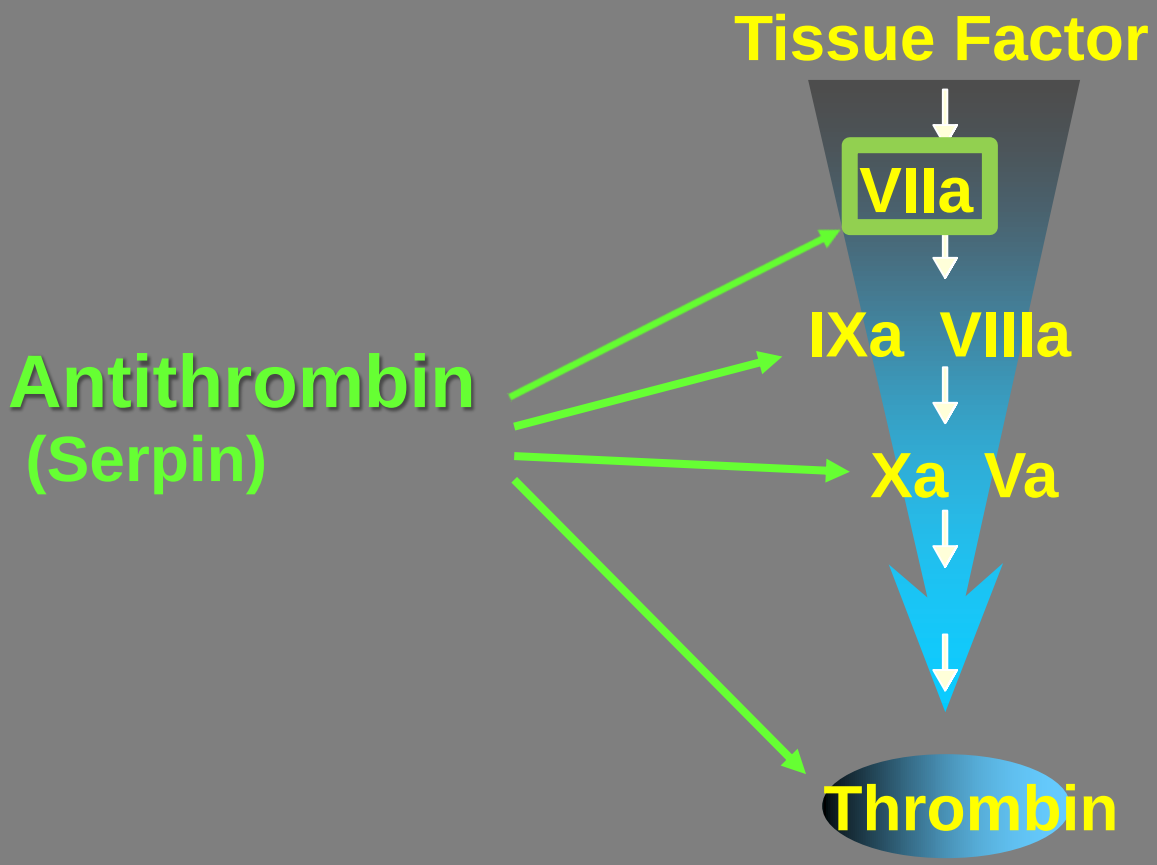
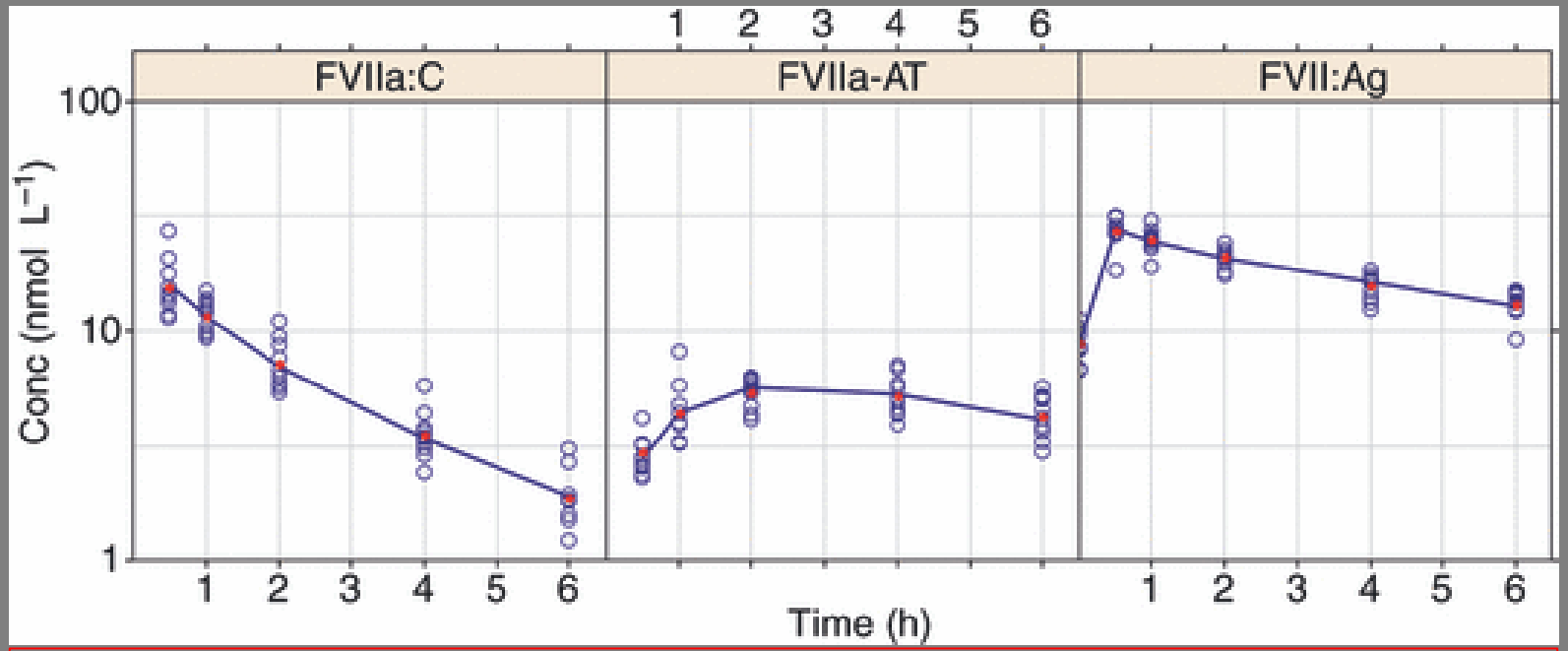
# Coagulation inhibition by Antithrombin



# The FVIIa AT Complex: milestones

- Antithrombin III (AT) inhibits FVIIa when bound to TF and not as free FVIIa *Lawson et al JBC 1993 Rao et al Blood 1993*
- Compared to TFPI, AT is a poor inhibitor of FVIIa-TF *Broze et al 1993 Blood 1993 Rao et Al Blood 1995*
- FVIIa-AT complex is relatively abundant in plasma (2% of plasma FVII antigen) *Smith et al. JTH 2007 (abst)*

# Recombinant human factor VIIa (rFVIIa) is cleared by antithrombin in hemophilia patients

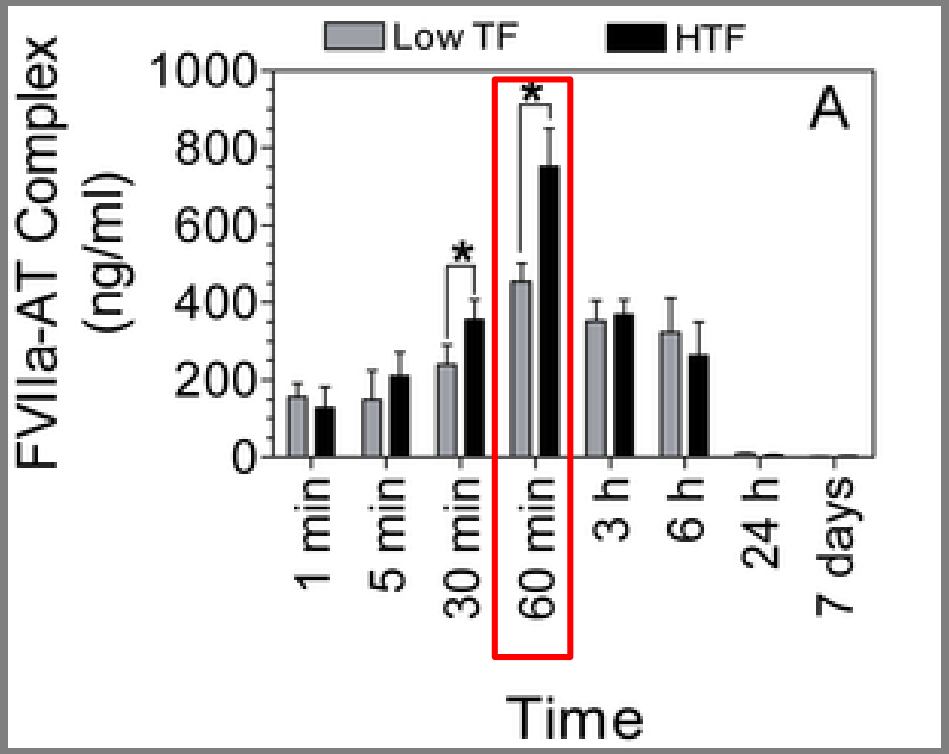



The rFVIIa-AT complex formation was responsible for 65% of the rFVIIa clotting activity clearance after administration in HA patients

**Journal of Thrombosis and Haemostasis** 2011 DOI: 10.1111/j.1538-7836.2010.04152.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2010.04152.x/full#f3

Agersø JTH 2011

# Levels of FVIIa-AT generated in vivo in “High TF and low TF” mice following administration of rFVIIa




Modest effect of TF on FVIIa-AT levels?

LPS administration caused a 600% increase in TF (HTF) but only 25% increase in FVIIa-AT complex concentration

Vatsyayan R, Kothari H, Mackman N, Pendurthi UR, Rao LVM (2014) Inactivation of Factor VIIa by Antithrombin In Vitro, Ex Vivo and In Vivo: Role of Tissue Factor and Endothelial Cell Protein C Receptor. PLoS ONE 9(8):

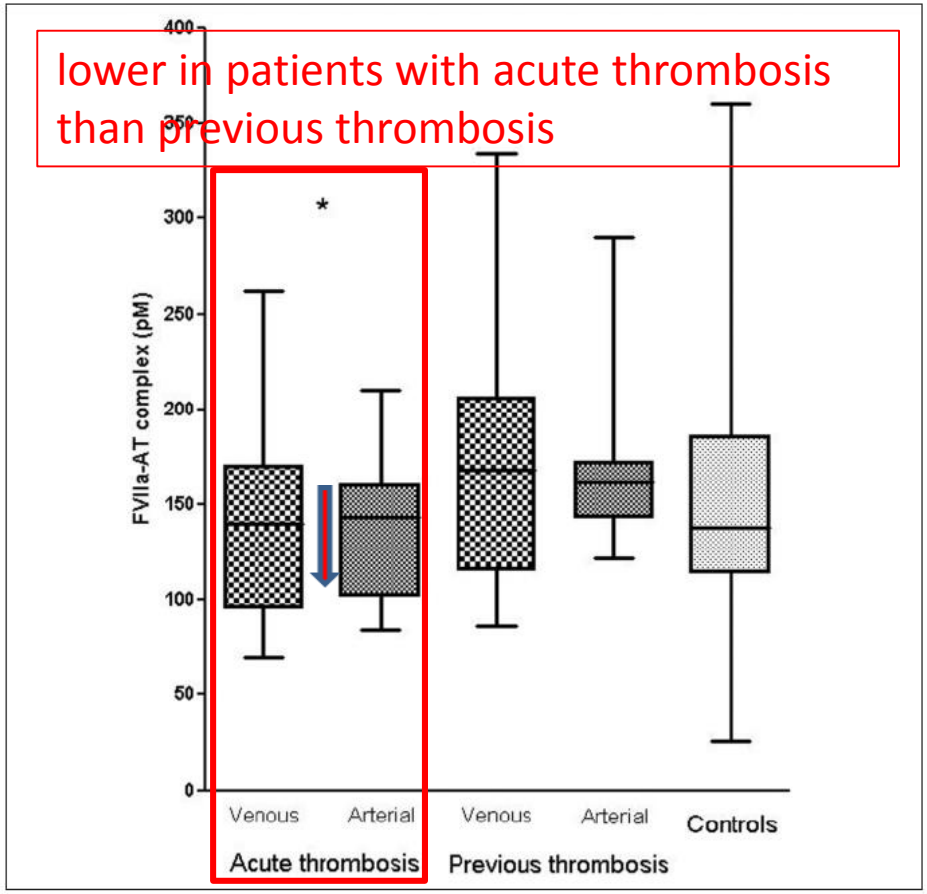
# The FVIIa AT Complex: open questions

TF, either circulating or intravascular, or some other factors in blood, are responsible for a relatively rapid inactivation of FVIIa by AT in vivo.

- Could AT be a significant regulator of FVIIa function and turnover?
- Which is the physiological significance of this inhibition?
- Is the circulating levels of FVIIa-AT complex an indirect indicator of intravascular TF exposure in vivo?

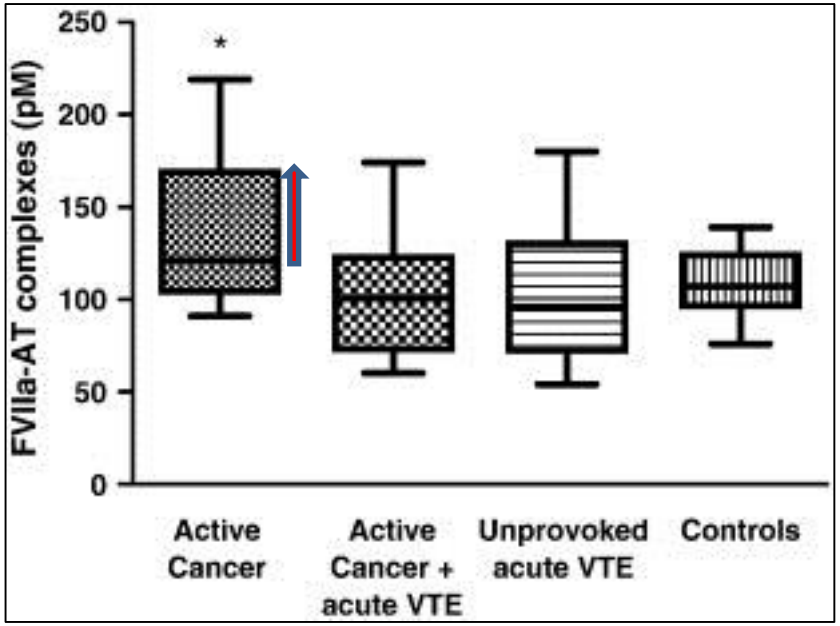
**Factor VIIa-antithrombin complexes in patients with arterial and venous thrombosis**

***Spiezia et al TH 2010***




**Factor VIIa-antithrombin complexes plasma levels in cancer patients with and without thrombosis**

***Spiezia et al Thr Res 2012***



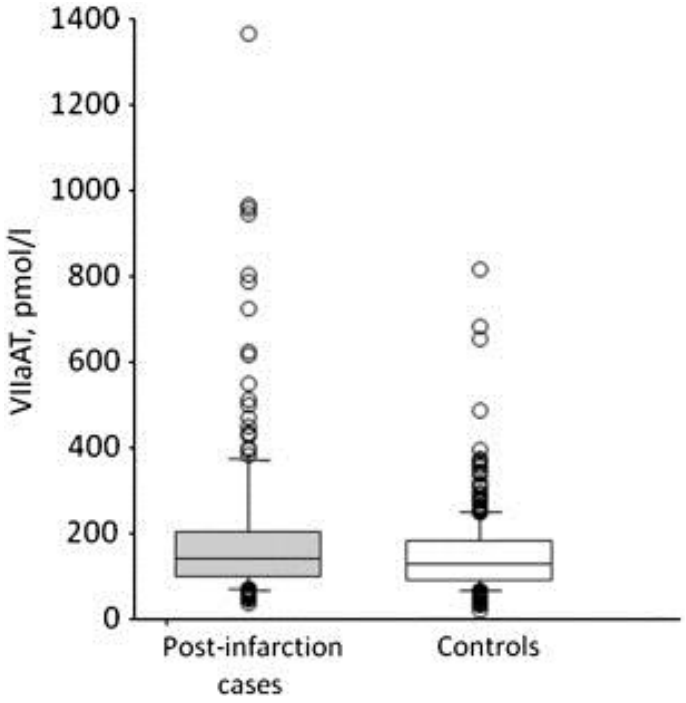

higher in patients with active cancer

# Relationships of plasma factor VIIa-antithrombin complexes to manifest and future cardiovascular disease

Silveira et al  Thrombosis Research  2012

”Slightly increased plasma VIIaAT concentrations observed after MI may reflect processes that occur in connection with the acute event…”

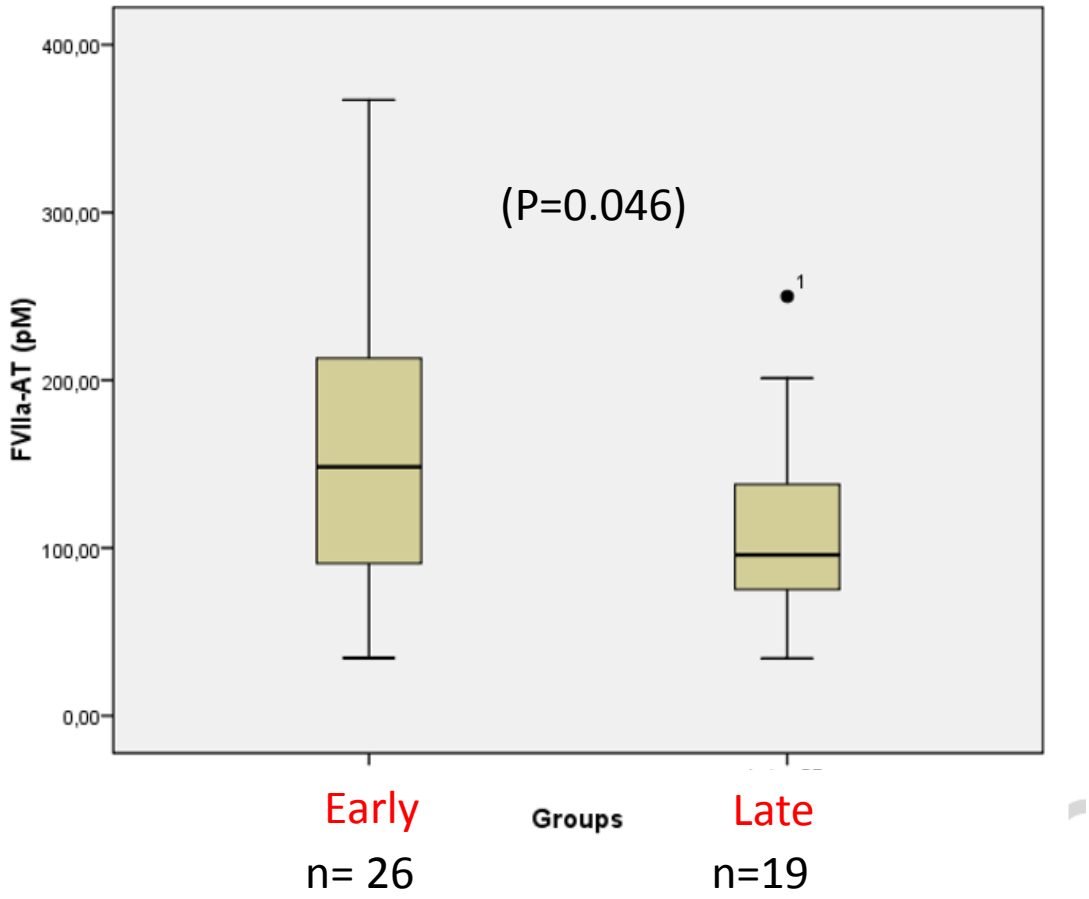
“Plasma VIIaAT concentration had no predictive value for future CVD in our study population”



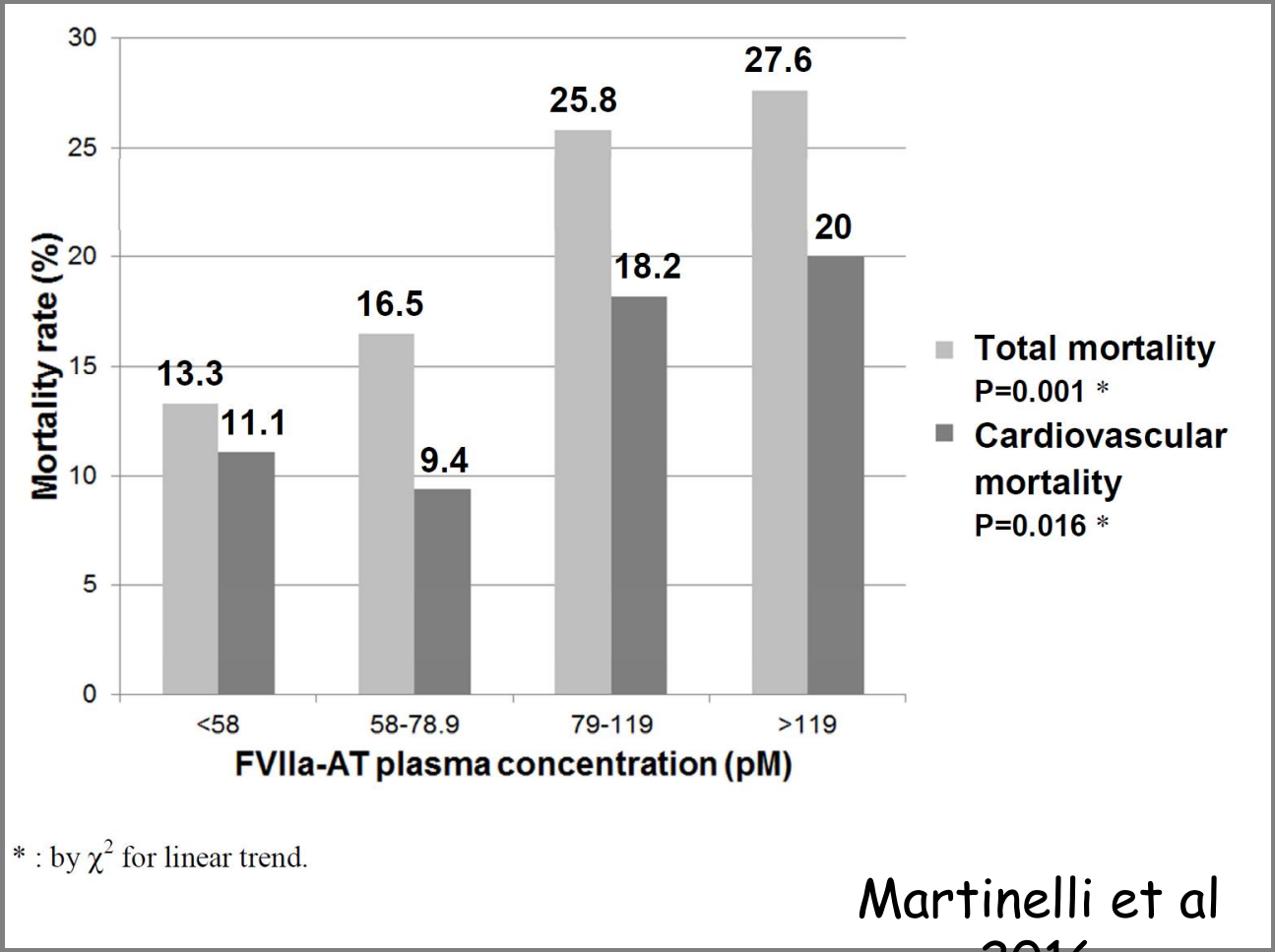

SCARF study

# FVIIa-AT plasma levels in early and late severe preeclampsia

**Luci Maria Sant Ana Dusse et Al  Clinica Chimica Acta  June 2017**

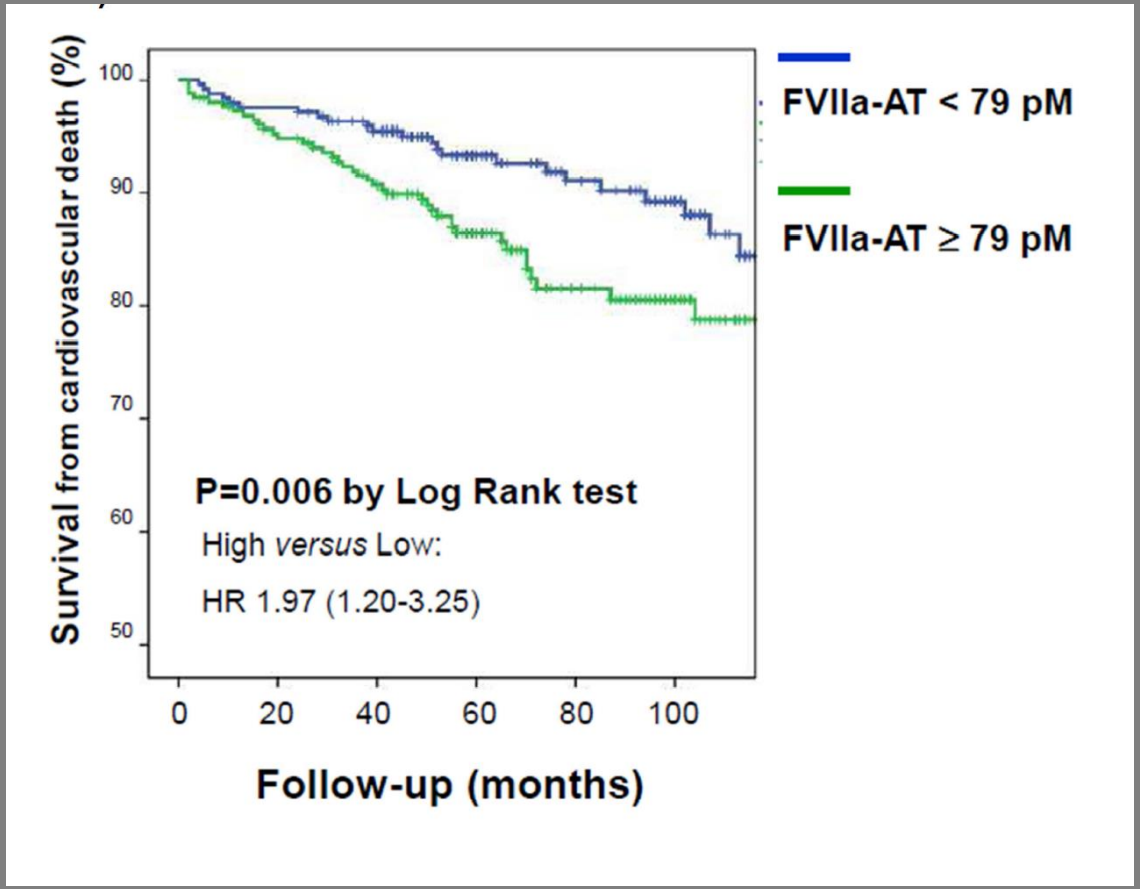


# The Factor VIIa - antithrombin complex concentration in plasma predicts mortality in patients with coronary atherosclerosis



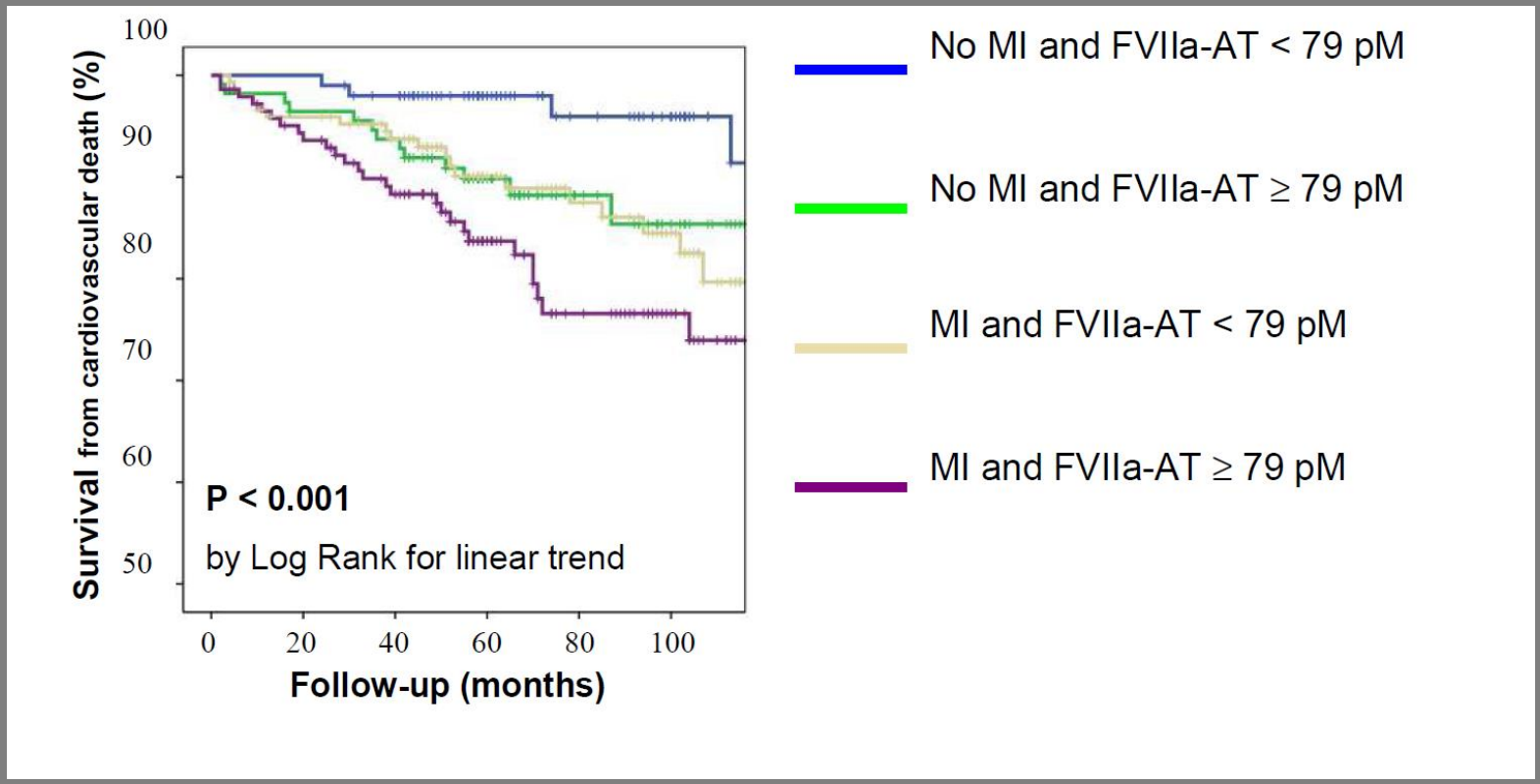

Martinelli et al 2016

# The Factor VIIa - antithrombin complex concentration in plasma predicts mortality in CAD patients



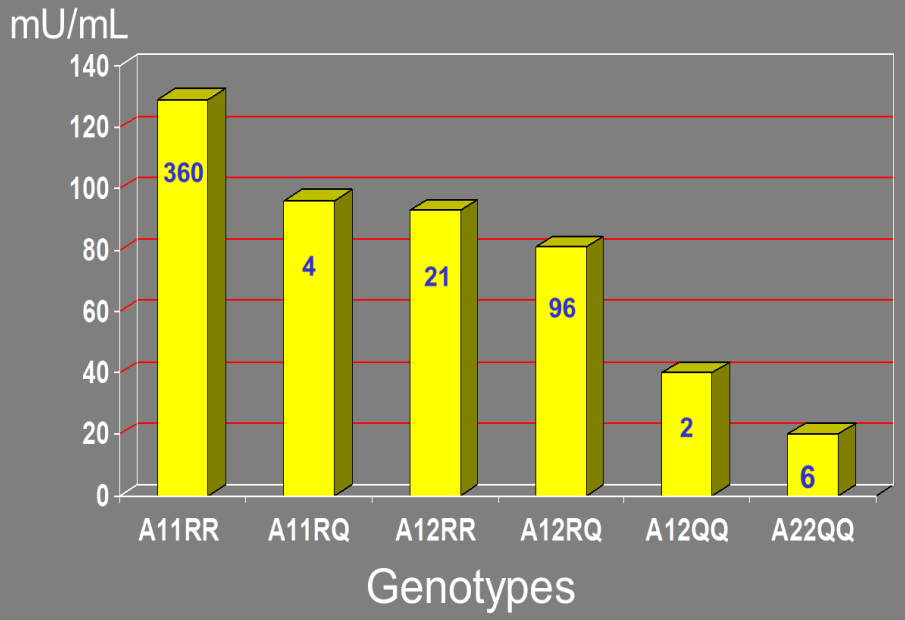

Martinelli et al 2016

# The Factor VIIa - antithrombin complex concentration in plasma predicts mortality in CAD patients with history of previous Myocardial Infarction

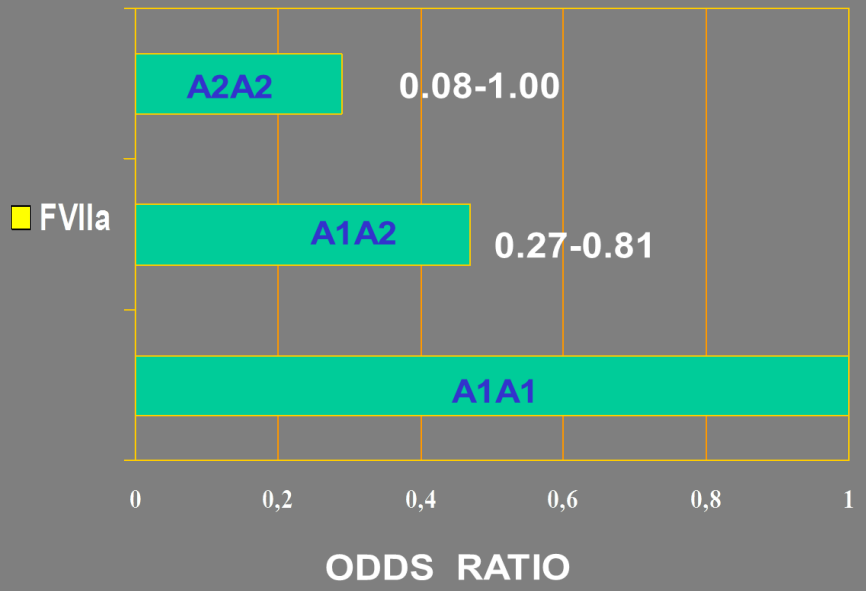



Martinelli et al 2016

# Contribution of *F7* Genotypes to FVII levels and Risk of Myocardial Infarction

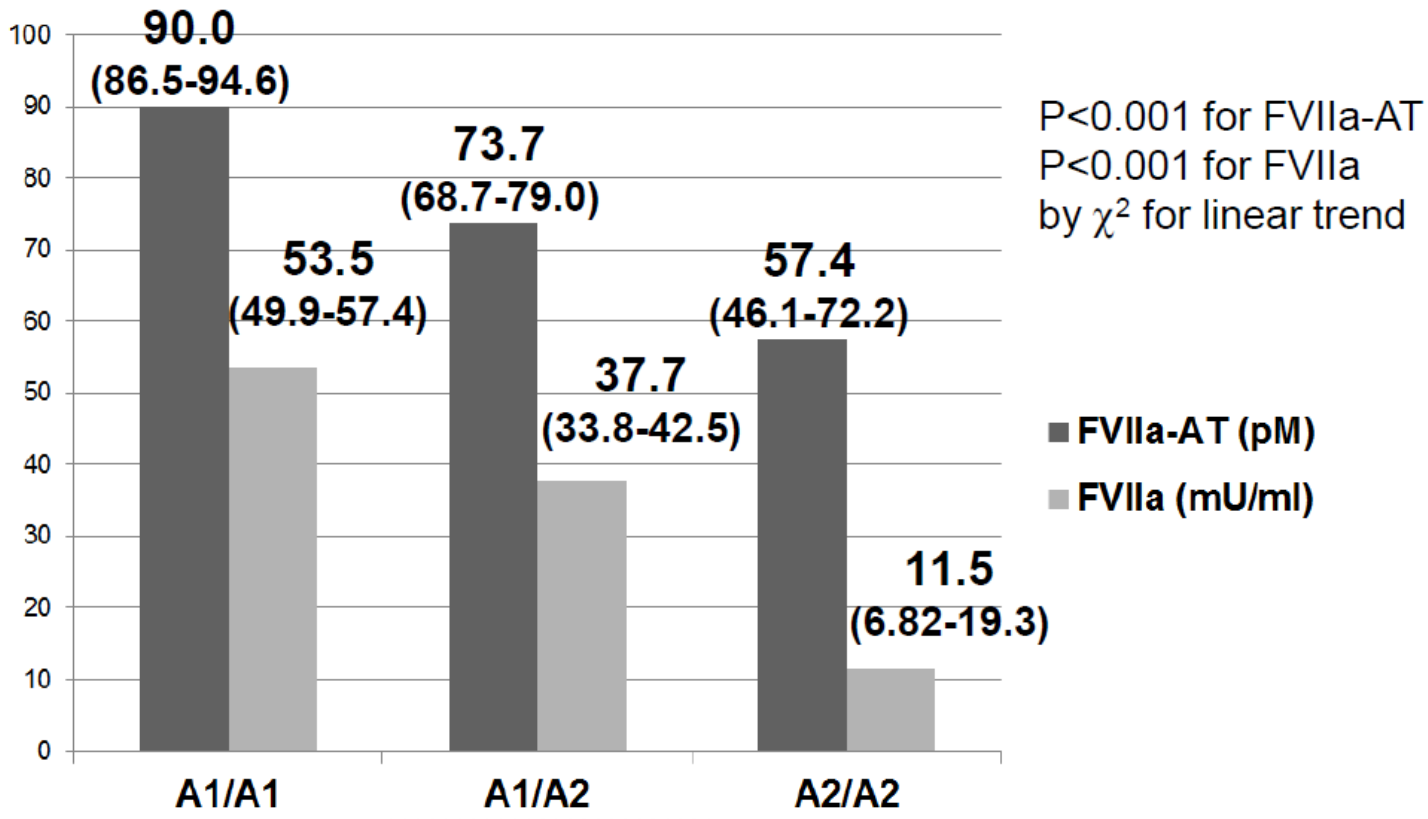



Bernardi et al ATVB, 1996




Girelli et al. N Engl J Med, 2000

# FVII genotypes predict FVIIa-AT complex levels

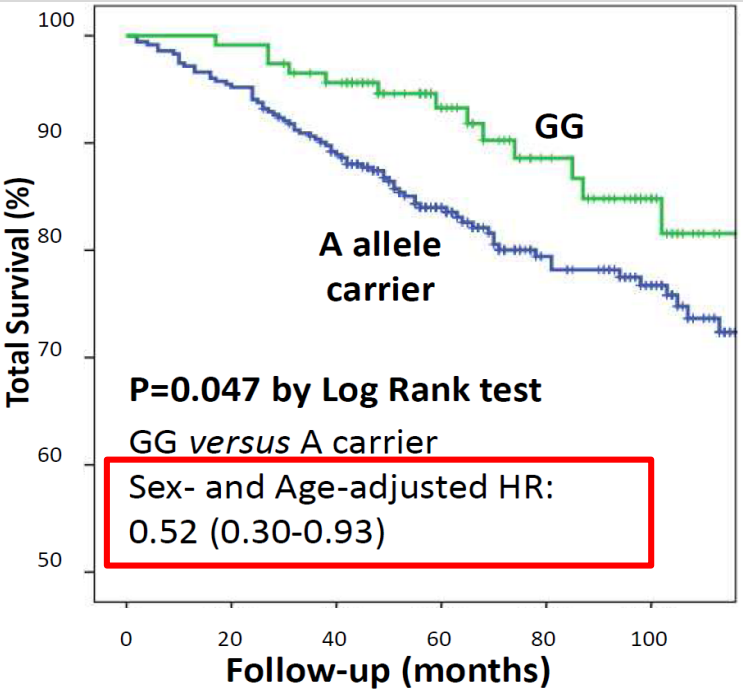


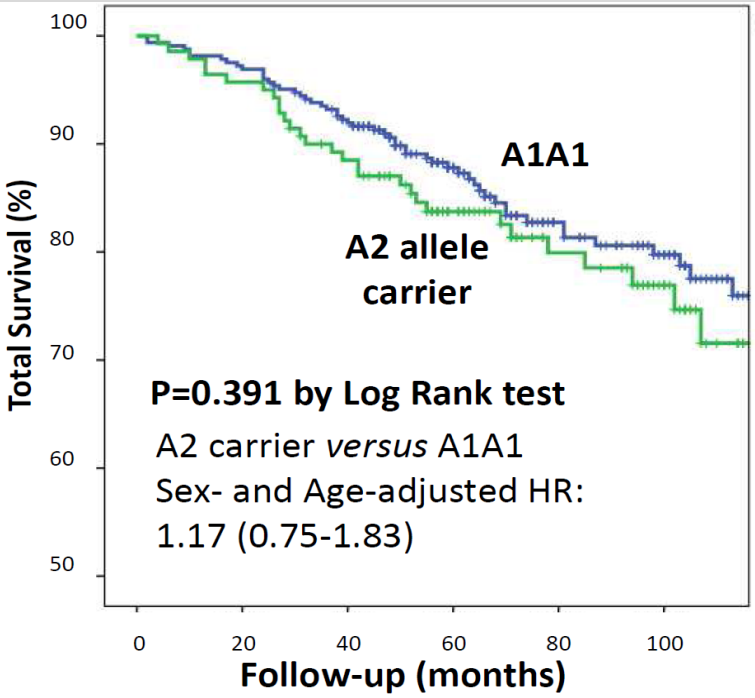
# TF genotypes predict FVIIa-AT complex levels

| | | n | FVIIa-AT | P * |
|---|---|---|---|---|
| **Carrier *TF* -603A allele** | Carrier A | 483 | 86.2 (82.4-90.1) | **0.013** |
| | GG | 161 | 77.0 (71.5-83.0) | |

# GENETIC DETERMINANTS OF FVIIa-AT PLASMA LEVELS AND SURVIVAL

| | TF | FVII |
|---|---|---|
| β-coefficient with 95%CI | -0.134 (-0.222 – -0.046) | -0.252 (-0.334 – -0.171) |
| | P=0.003 | P<0.001 |



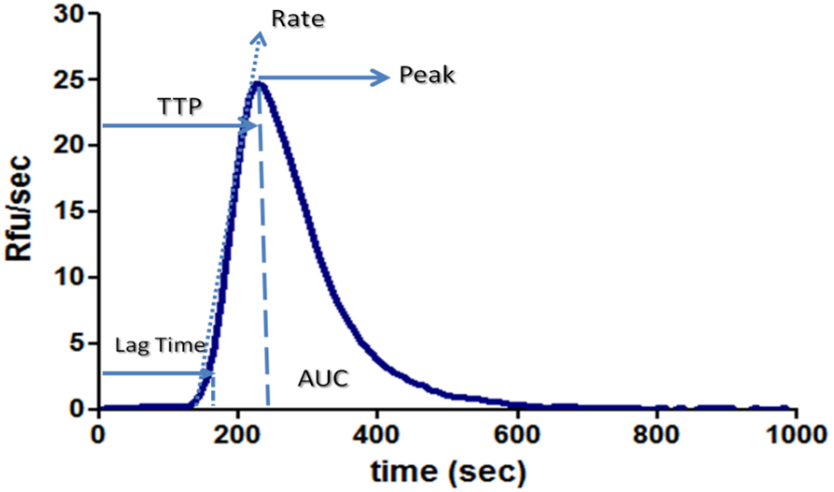



# What about function?

# Thrombin generation parameters and FVIIa-AT levels

| | FVIIa-AT < 79 pmol L$^{-1}$ ( *n* = 122) | FVIIa-AT ≥ 79 pmol L$^{-1}$ ( *n* = 150) | *P* † |
|---|---|---|---|
| Lag time (s) | 56.3 (54.1–58.0) | 57.4 (55.7–59.2) | NS |
| Time to peak (s) | 142.6 (139.8–146.9) | 141.2 (138.4–144.0) | NS |
| Peak (Rfu/s) | 6.36 (6.17–6.55) | 6.82 (6.55–7.03) | 0.009 |
| ETP (Rfu) | 854.1 (837.2–871.3) | 906.9 (880.1–925.2) | 0.001 |

The median level (79 pmol L–1 ) was used as threshold value.




High plasma levels of FVIIa-AT are associated with an increased thrombin generation (Peak and ETP)

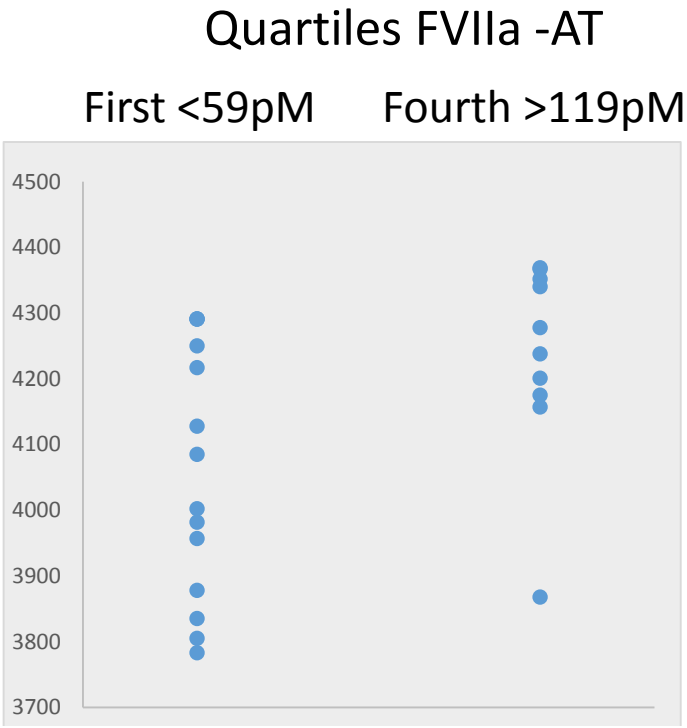
Martinelli et al 2016

# FXa generation in CAD patients' plasma

Is FXa generation (at low TF concentration) able to reveal hypercoagulability features in relation to the FVIIa-AT concentration?

AUC (Rfu)

(P=0.007*)




FXa generation is higher in patients with high FVIIa-AT complex levels in plasma

*By ANOVA with polynomial contrasts for linear trend, confirmed after adjustment for traditional cardiovascular risk factors

# FVIIa-AT complex levels, cardiovascular risk and hypercoagulability

## CONCLUSIONS(1)

- **High FVIIa-AT levels were associated with a greater risk of mortality in patients with stable CAD. A larger increase of FVIIa-AT levels was associated with non-fatal cardiovascular events during the follow-up**

↓

**FVIIa-AT complex levels may predict long term outcomes in the setting of secondary prevention of CAD**

- **High FVIIa-AT levels correlated with an increased thrombin generation with an increased FXa generation, particularly in the early phase**
- **FVIIa-AT levels were strongly associated with the concentration of Apo C-III, a recognized risk factor for ischemic heart disease**

# FVIIa- AT complex levels, genotypes and cardiovascular risk

## CONCLUSIONS(2)

- ***F7*** **and TF Genotypes predict FVIIa-AT levels in plasma**
- **Only TF Genotypes were associated with risk of mortality in patients with stable CAD**

- **The chr 11 SNP rs964184 -tagging APOC3 locus and susceptibility to CVD- may influence FVIIa-AT levels (consistent with the effect on Apo C-III concentration)**

**Genetic and biochemical findings indicate FVIIa-AT complex levels as marker of hypercoagulability and cardiovascular risk mediated by TF and lipoprotein/lipid components**

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