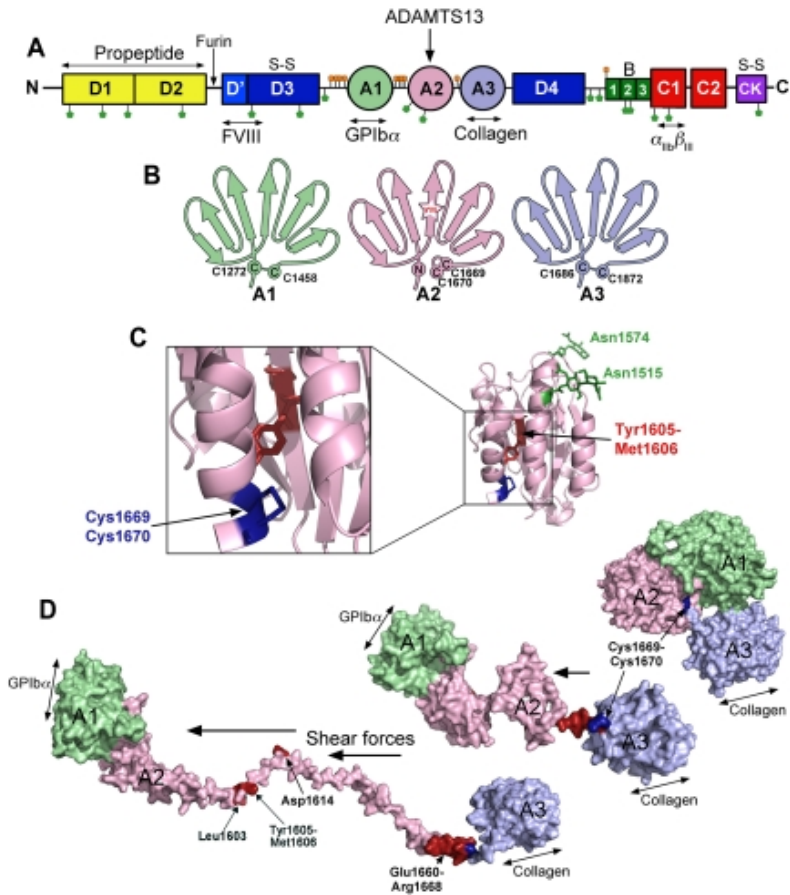


# The vWF/ADAMTS-13 Axis in Thrombosis-Hemostasis and Beyond

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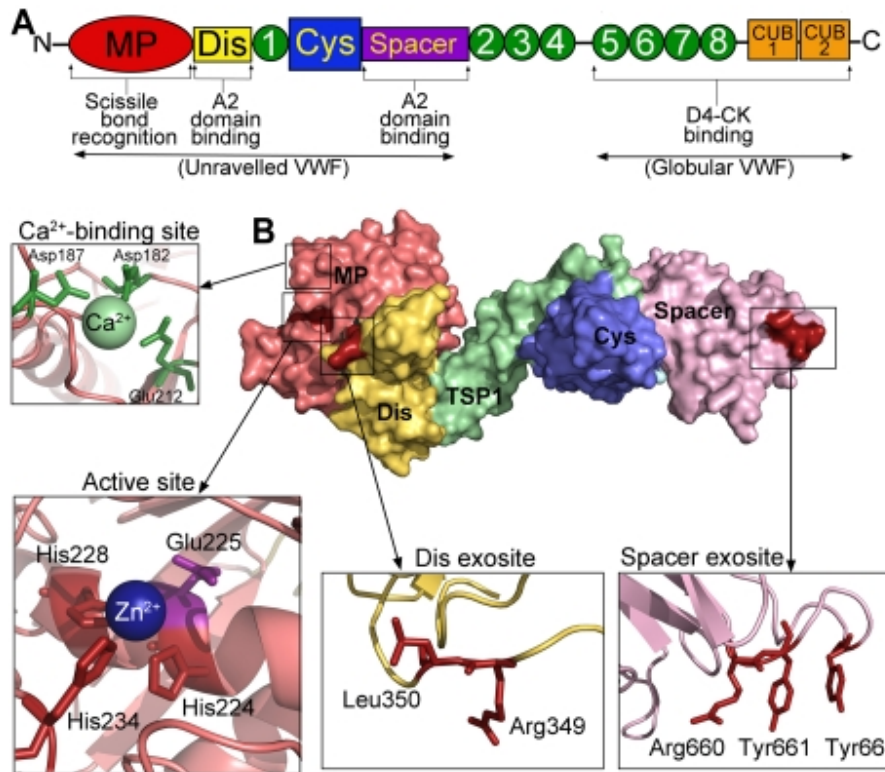
# The substrate, VWF

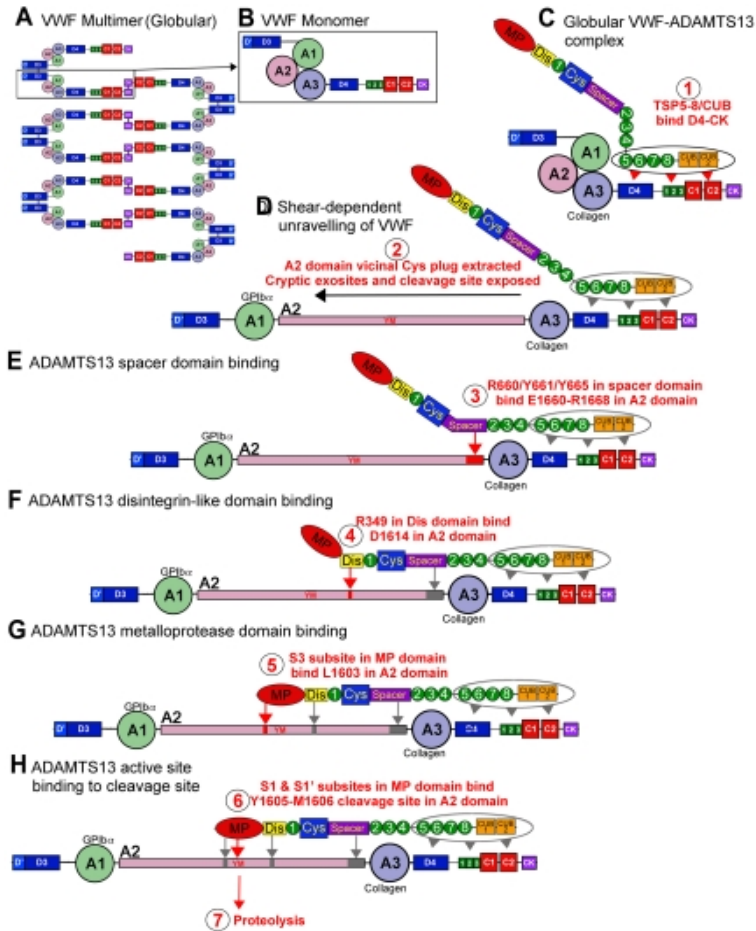
- von Willebrand factor (VWF) is a large adhesive glycoprotein with established functions in hemostasis.
- Synthesis of VWF is restricted to endothelial cells and megakaryocytes.
- Each polypeptide monomer (~ 310 kDa) has a signal peptide, a propeptide and the mature VWF that contains a variety of specific ligand binding sites
- dimerization of VWF monomers takes place in the endoplasmic reticulum, through intermolecular disulphide pairing of Cys residues in the cysteine knot domain.
- Multimerization of the dimers in the Golgi, is a process catalyzed by the propeptide (D1 and D2 domains), which acts as a protein disulphide isomerase to form disulphide bonds between the N-termini of VWF dimers.
- the mature multimeric VWF is stored in Weibel-Palade bodies of endothelial cells or  $\alpha$ -granules of platelets in UL form
- UL-VWF multimers can be released constitutively from the endothelium into the bloodstream, or on demand
- VWF released from endothelial cells remains tethered to the cell surface or free in circulation, VWF adopts its globular conformation .



# The protease, ADAMTS13

- ADAMTS13 is synthesized in hepatic stellate cells and vascular endothelial cells-as an ~ 180-kDa glycoprotein.
- ADAMTS13 is a member of the ADAMTS family of Zn<sup>2+</sup>-dependent metalloproteases, which all contain ( N-terminus) a metalloprotease, disintegrin-like, thrombospondin type 1 (TSP) repeats, cysteine-rich and spacer domains.
- ADAMTS13 has a plasma half-life of 2 to 3 days, with 3% to 5% of ADAMTS13 circulating bound to VWF
- is constitutively active
- protease activity of ADAMTS13 is controlled not by natural inhibitors but by conformational changes in its substrate, which are induced when VWF is subject to elevated rheologic shear forces.
- is able to reduce the size and hemostatic function of VWF in vivo by controlled cleavage at a single, specific site ( scissile bond, Tyr1605-Met1606) within the VWF A2 domain.





- VWF circulate in its globular/ADAMTS-13-resistant form until it encounters a site of vessel damage results in the exposure of subendothelial collagen to the flowing blood this transforms VWF from a globular to an elongated protein
- Under these conditions, circulating globular VWF can bind rapidly to exposed collagen via its A3 domain, which tethers the globular form to the vessel wall.
- The tethered VWF is now exposed to elevated shear forces, which induces the unraveling of the molecule into its string-like conformation.
- This exposes platelet-tethering sites in the VWF A1 domain, captures circulating platelets to the site of vessel damage enabling primary platelet plug formation
- This conformational transformation unfolds the VWF A2 domain and reveals the scissile bond.

# Arterial thrombosis

- coronary heart disease and ischemic stroke
- is associated with a high mortality and morbidity in the Western World
- Previous studies have suggested a role for Von Willebrand Factor (VWF) in the pathogenesis of arterial thrombosis.
- Circulating VWF is almost completely of endothelial origin and in case of endothelial damage, plasma levels of VWF increase with increase of UL
- Therefore VWF is considered as a marker of endothelial damage or dysfunction
- ADAMTS13 degrades VWF multimers into smaller, less procoagulant forms
- Multiple risk factors for arterial thrombosis are known, including the classical risk factors hypertension, diabetes and obesity
- Many studies have shown that the variation in coagulation factors may also confer a higher risk of arterial thrombosis
- Hypothetically, lower levels of ADAMTS13 are associated with increased VWF activity and can thereby contribute to arterial thrombosis.

# Von Willebrand factor and ADAMTS13 in arterial thrombosis: a systematic review and meta-analysis

- Studies found a positive association between VWF and coronary heart disease
- Same results the large prospective ARIC study (included 1802 CHD cases aged 45 – 64 y)
- Same results many case-control studies, suggesting a pathogenic role for VWF in coronary heart disease
- most studies have measured VWF:Ag levels However, it might be possible that not the concentration of VWF is associated with coronary heart disease, but rather the functional activity of VWF
- data allow the conclusion that high VWF levels are associated with an increased risk of CHD

**Table 1**  
Prospective cohort studies on the association between Von Willebrand Factor and coronary heart disease (CHD) or myocardial infarction (MI).

Study	N	Mean follow-up time	VWF level (IU/ml) in cases	VWF level (IU/ml) in controls	P-value	Disease endpoint OR [95% CI]
ARIC study [30]	14904	n.a.	White men: 1.22 ± 2 Black men: 1.34 ± 4 White women: 1.15 ± 2 Black women: 1.39 ± 3 0.77 (0.71-0.84)	White men: 1.11 ± 1 Black men: 1.30 ± 2 White women: 1.11 ± 1 Black women: 1.34 ± 1 0.75 (0.73-0.77)	White men: P < 0.05 White women: P < 0.05	Men: 1.12 P < 0.05 Women: 1.02, NS
NPHS [50]	1393	16.1 years	n.a.	n.a.	NS	Fatal IHD: 1.34 [1.00-1.79] Non fatal IHD: 0.89 [0.59-1.33] Total IHD: 1.16 [0.92-1.47] RR men 1.05 [0.91-1.20] RR women 1.02 [0.84-1.25] MI: 0.95 [0.81-1.12] AP: 1.00 [0.80-1.25] 2.58 [0.87-7.63]
ARIC study [1]	14477	4-7 years	n.a.	n.a.	n.a.	n.a.
Edinburgh artery study [4]	1592	5 years	1.15 (0.82-1.56)	1.05 (0.78-1.38)	P < 0.05	n.a.
VIP and MONICA study [57]	234	n.a.	Men: 1.42 Women 1.62	Men: 1.31 Women: 1.34	NS P = 0.044	1.20 [1.01-1.43] 1.53 [1.10-2.12]
Caerphilly heart study [21]	1997	61 months	1.28 ± 0.44	1.19 ± 0.42	P = 0.0003	1.11 [0.97-1.27]
British regional heart study [19]	1891	n.a.	1.21 ± 0.43	1.13 ± 0.44	n.a.	HR 1.09 [0.85-1.45]
Reykjavik study [29]	6428	17.5 years	n.a.	n.a.	n.a.	HR 1.34 [1.07-1.67]
Caerphilly study [51]	2223	13.4 years	n.a.	n.a.	n.a.	HR 0.97 [0.69-1.37]
PRIME study [22]	296	n.a.	n.a.	n.a.	n.a.	1.33 [1.02-1.74]
BWHHS [52]	3582	4.7 years	1.44 (1.16-1.78)	1.39 (1.12-1.75)	P = 0.21	1.24 [0.56-2.73]
Edinburgh artery study [25]	1592	17 years	CVD: 1.15 (0.87-1.48) MI: 1.16 (0.87-1.55)	CVD: 1.05 (0.78-1.37) MI: 1.05 (0.78-1.37)	P < 0.001 P < 0.001	n.a.
Fletcher challenge study [56]	720	n.a.	1.40 ± 0.61	1.27 ± 0.52	n.a.	ACS: 2.43 [1.31-4.51] AP: 0.87 [0.43-1.79]
FRIM study [28]	AP: 321 ACS: 486	5 years	AP: 1.11 (0.85-1.47) ACS: 1.17 (0.91-1.50)	AP: 1.16 (0.88-1.41) ACS: 1.14 (0.84-1.40)	P = 0.71 P = 0.005	MI: 1.24 [0.87-1.76]
British regional heart study [23]	3217	7 years	MI: 1.46 AP: 1.38	MI: 1.37 AP: 1.37	P = 0.005 P = 0.87	HR 1.19 [1.04-1.37] CHD: 1.58 [0.29-8.57] MI: 1.52 [0.75-3.10] SCD: 3.34 [2.26-4.93] NSCD: 2.11 [1.40-3.19] MI: 1.40 [1.17-1.67]
Three City study (3C) [53]	1254	4 years	1.44 (1.19-1.67)	1.30 (1.10-1.58)	P = 0.046	n.a.
ARIC study [24]	14009	12 years	Incidence rate: SCD: 19.8 (16.2-23.4) NSCD: 14.9 (11.8-18) MI: 51.1 (45.5-56.8)	n.a.	n.a.	1.21 [1.02-1.43] HR 1.39 [0.98-1.76] MI: 1.52 [0.75-3.10] SCD: 3.34 [2.26-4.93] NSCD: 2.11 [1.40-3.19] MI: 1.40 [1.17-1.67]
WVF-HF [27]	1064	7.1 and 5.6 years	0.99 (0.73-1.39)	0.90 (0.66-1.19)	P < 0.0001	1.21 [1.02-1.43]
Rotterdam Study [54]	5801	6.4 years	1.42 ± 0.8	1.30 ± 0.6	n.a.	HR 1.39 [0.98-1.76]
Rotterdam Study [55]	5933	n.a.	n.a.	n.a.	n.a.	HR 1.2 [0.9-1.6]
VIP and MONICA study [26]	1364	n.a.	1.60 (1.27-2.03)	1.41 (1.13-1.79)	P < 0.001	2.52 [1.72-3.67]
Reykjavik study [20]	5541	19.4 years	n.a.	n.a.	n.a.	1.08 [1.02-1.15]

**Table 2**  
Case-control studies on the association between Von Willebrand Factor and coronary heart disease (CHD) or myocardial infarction (MI).

Participants	N total (% cases)	Blood sampling after event	Mean follow-up time	VWF level (IU/ml) in cases	VWF level (IU/ml) in controls	P-value	Disease endpoint OR [95% CI]
First ever MI [11]	1186 (46)	0 months	n.a.	1.38 ± 0.51	1.35 ± 0.66	NS	1.44 [1.00-2.07]
First ever MI [89]	106 (47)	Acute and 8.4 years	8.4 years	Acute: 1.36 (1.13-1.61) Chronic: 1.86 (1.39-2.27) 38 event (235-536)	Acute: 1.36 (0.97-1.67) Chronic: 1.72 (1.36-2.14) 382 event (267-453)	n.a. significant P = 0.003	Acute: 0.99 [0.4-2.5] Chronic: 1.64 [0.4-2.8] 2.01 [1-3.8]
First ever MI [12]	135 (41)	0-3 days	n.a.	1.08 (0.80-1.47)	0.8 (0.60-1.07)	n.a.	4.2 [2.2-8.0]
First ever MI [13]	843 (24)	23-146	n.a.	Men: 1.4 ± 0.55 Women: 1.02 ± 0.39	Men: 1.0 ± 0.41 Women: 1.00 ± 0.35	n.a.	n.a.
MI [9]	281 (53)	3-5 months	n.a.	n.a.	n.a.	P = 0.01	n.a.
MI [14]	121 (37)	3 months after discharge	4.9 years	1.76 (1.56-1.96)	1.41 (1.31-1.55)	P < 0.001	8.015 P < 0.001
MI or SAP [3]	MI: 223 (57) SAP: 123 (58)	At inclusion and 12 months	2 years	MI: 1.77 (0.70-1.22) SAP: 1.54 (0.90-1.95)	MI: 1.24 (0.56-1.61) SAP: 1.27 (0.48-1.29)	P = 0.008 P = 0.026	MI: 1.80 [1.18-2.60] SAP: 1.78 [0.7-2.95]
MI or AP [15]	AMI: 46 (36) AP: 42 (24)	Within 8 hours	n.a.	AMI: 1.36 ± 0.114 AP: 1.06 ± 0.099	1.02 ± 0.088	P < 0.001	n.a.
MI [9]	111 (33)	6 weeks	46 months	1.36 ± 0.39	1.22 ± 0.36	F = 0.001	n.a.
MI [23]	1048 (78)	2 months	26 months	1.58 ± 0.74	1.46 ± 0.68	NS	n.a.
MI [9]	194 (76)	n.a.	2 years	1.16 (0.82-2.24)	1.13 (0.47-3.30)	F = 0.70	89.14 [0.36-5.5]
MI [27]	347 (23)	3 months	2-3 years	Men: 1.09 ± 0.77 Women: 1.06 ± 0.43	Men: 1.34 ± 0.54 Women: 1.35 ± 0.48	n.a.	2.3 [1.3-4.0]
MI [81]	71 (42)	Acute	n.a.	Men: 2.15 ± 0.97	Men: 1.35 ± 0.48 Women: 1.43 ± 0.76	P < 0.0001	3.57 [0.88-7.51]
MI [28]	828 (24)	3 year	n.a.	1.24	1.07	P < 0.0001	4.7 [2.3-9.7]
MI or UAP [39]	AMI: 80 (71) UAP: 159 (86)	Acute	n.a.	AMI: 1.39 ± 0.095 UAP: 1.15 ± 0.0456	0.95 ± 0.095	P = 0.05	n.a.
MI [40]	132 (28)	Admission, 1.37-14 days	n.a.	n.a.	n.a.	P < 0.0001	day 0: 1.11 [0.63-1.96] day 3: 1.46 [1.06-2.01]
MI [41]	950 (49)	3-9 months	n.a.	1.86 ± 0.68	1.64 ± 0.60	P < 0.0001	n.a.
MI [42]	56 (46)	At PCI and chronic phase	n.a.	1.51 ± 0.58	2.05 ± 0.90	n.a.	n.a.
MI [43]	237 (60)	3 months	n.a.	1.13 (0.82-1.44)	1.06 (0.70-1.37)	F = 0.032	1.04 [0.99-1.01]
MI [27]	142 (29)	3 months	n.a.	1.20 ± 0.30	1.32 ± 0.32	F = 0.242	0.79 [0.25-2.47]
MI or UAP [59]	649 (42)	1-3 months	4.2 years	1.19 ± 0.7	1.06 ± 0.4	n.a.	1.2 [0.81-0.23]
ACS or SAP [49]	ACS: 100 (34) SAP: 154 (50)	Acute	n.a.	ACS: 1.77 ± 0.48 SAP: 1.43 ± 0.29	1.41 ± 0.80	P = 0.05	n.a.
ACS [75]	156 (21)	Acute and 48 hours	30 days and 1 year	ACS: 2.15 ± 0.59 CAD: 1.47 ± 0.32	vs. 1.21 ± 0.20	n.a.	1.02 [1.00-1.03] HR: 14.4 P = 0.001
ACS [62]	155 (34)	Acute	n.a.	2.85 ± 1.27	1.05 ± 0.26	F = 0.01	HR: 10.0 [3.0-10.9]
CHD [43]	791 (29)	n.a.	n.a.	1.46 (1.20-1.68)	1.31 (1.10-1.46)	F = 0.0002	1.5 [1.3-2.4]
CHD [44]	386 (50)	16 days and 6 months	n.a.	1.59 (1.27-1.94)	1.26 (1.00-1.60)	P < 0.001	P = 0.001
CAD [54]	229 (41)	Within 12 hours	n.a.	0.505 (0.601-0.513)	0.40 (0.403-0.407)	NS	n.a.
CAD [10]	141 (73)	Before FICA	13.2 months	0.679 (0.45-1.14)	0.989 (0.37-0.96)	F = 0.58	2.5 [0.5-13.3]
CAD [45]	325 (89)	At angiography and 2-14 days	22.3 months	1.86 (1.45-2.39)	1.03 (1.33-2.15)	F = 0.041	HR: 3.3 [1.9-5.4]
CVD [46]	559 (46)	1-3 months	n.a.	1.20 (0.8-1.4)	1.06 (0.8-1.4)	n.a.	2.1 [1.3-3.5]
AF [47]	2806 (3.8)	2 years	n.a.	1.38 ± 0.49	1.25 ± 0.49	F = 0.05	1.34 [1.00-1.53]
Nonvascular AF [48]	594 (8.1)	At inclusion	n.a.	n.a.	n.a.	n.a.	HR: 2.5 [1.2-5.0]
Intermittent claudication [54]	363 (44)	n.a.	6-7 years	Total IHD: 1.43 (0.99-1.90) Fatal IHD: 1.51 (0.96-1.88)	1.23 1.06-1.60	P = 0.05	1.04 [0.90-1.19]

# VWF and ischemic stroke

- An association between high VWF levels and ischemic stroke has been found in most studies
- meta-analysis of all prospective cohort studies, consisting of 1567 cases, on the association between VWF and ischemic stroke and found an odds ratio of 1.17 [95% CI 1.08–1.26] if included the case-control studies, of in total 2532 patients, in the meta-analysis OR of 1.55 (95% CI 1.31–1.83)
- Lip et al., VWF levels were found to be significantly higher in ischemic stroke patients who died, when compared with patients who were still alive at 12 months follow-up

Figure 1. Forest plot of the association between VWF and ischemic stroke

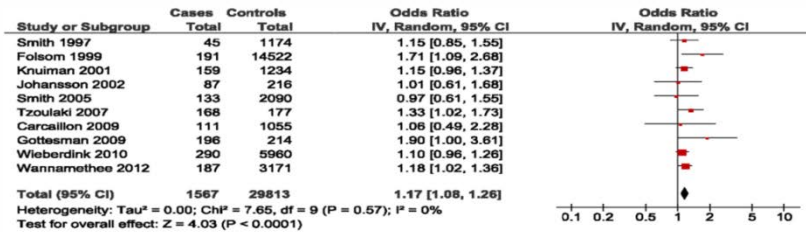


Table 4  
 Case-control studies on the association between Von Willebrand Factor and ischemic stroke.

Participants	N total (% cases)	Blood sampling after event	Mean follow-up time	VWF level (IU/ml) in cases	VWF level (IU/ml) in controls	P-value	Disease endpoint OR (95% CI)
First ever ischemic stroke [88]	405 (49)	Within 7 days and 3–6 months		Baseline: 1.84 Chronic: 1.78	Baseline: 1.64 Chronic: 1.64	P = 0.17 P = 0.21	2.8 [1.5–5.2]
First ever ischemic stroke [85]	249 (50)	7–14 days		1.47 ± 0.66	1.23 ± 0.5	P = 0.002	3.2 [1.4–7.5]
First ever ischemic stroke or TIA [82]	197 (48)	7–14 days		VWF:Ag: 1.32 (0.98–1.85) VWF:Act: 1.2 (0.9–1.8)	VWF:Ag: 1.22 (0.84–1.56) VWF:Act: 1.3 (0.9–1.7)	P = 0.04 NS	na.
First ever ischemic stroke or TIA [77]	549 (50)	7–14 days and 3 months		1.47 ± 0.68 1.25 ± 0.56	1.25 ± 0.5	P = 0.03 P < 0.001	1.9 [1.0–3.3] 1.9 [1.1–3.1] 6.7 [3.2–13.8]
First ever ischemic stroke [33]	813 (22)	23–146 months		1.0	1.1	na.	na.
Ischemic stroke [79]	40 (48)	72 hours		1.85 ± 0.67	1.34 ± 0.50	P < 0.05	na.
Ischemic stroke [80]	392 (53)	Within 10 days and 3–4 months	6 months or till death	Acute: 1.86 (1.75–1.97) Chronic: 1.51 (1.42–1.60)	Acute: 1.26 (1.19–1.33) Chronic: 1.26 (1.19–1.33)	P = 0.0001 P = 0.0001	na.
Ischemic stroke [78]	196 (83)	na.		1.44 ± 0.21	1.14 ± 0.16	P = 0.0002	na.
Ischemic stroke [91]	114 (65)	3–10 days and 1–3 months		Acute: 2.31 ± 0.90 Chronic: 1.98 ± 1.03	Acute: 1.41 ± 0.41 Chronic: 1.41 ± 0.41	P < 0.001 P < 0.01	na.
Ischemic stroke [83]	138 (60)	Within 48 hours and after 1 month		Acute: 1.78 (1.26–2.05) Chronic: 1.80 (1.55–2.15)	Acute: 1.33 (1.02–1.66) Chronic: 1.33 (1.02–1.66)	P < 0.001 P < 0.001	na.
Ischemic stroke [81]	121 (71)	At admission, 48 hr, 1 week, 2 weeks, 3 and 6 months	12 months	1.51 ± 0.39	1.00 ± 0.28	P < 0.0001	na.
Ischemic stroke [90]	296 (28)	Acute		na.	na.	na.	20.14 [6.61–85.39]
Ischemic stroke [86]	243 (49)	Acute		1.00 (0.66–1.00)	0.40 (0.30–0.80)	P = 0.0001	na.
Ischemic stroke [84]	1200 (50)	Within 10 days and 3 months		na.	na.	P < 0.0001	Acute: 1.87 [1.54–2.27] Chronic: 1.36 [1.15–1.62]
TIA or cerebral infarct or cerebral embolism [87]	CVA: 68 (50) TIA: 22 (50) CE: 18 (50)	na.		CVA: 2.08 ± 0.59 TIA: 1.78 ± 0.95 CE: 1.03 ± 0.40	CVA: 0.998 ± 0.26 TIA: 0.99 ± 0.28 CE: 0.98 ± 0.26	P < 0.001 P < 0.02	na.
TIA or minor ischemic stroke [97]	331 (29)	At least 4 weeks		1.37 ± 0.65	1.15 ± 0.57	P = 0.004	1.42 [0.57–3.52]
Non-valvular AF [48]	994 (39)	At inclusion		na.	na.	na.	RR 2.3 [1.0–5.6]
Non-valvular AF with ischemic stroke [102]	91 (67)	Within 48 hours and on day 7, 21 and 90	8.8 months	0.97 ± 0.16	0.92 ± 0.14	P = 0.202	na.
Non-valvular AF [89]	373 (137)	72 hours	3 years	na.	na.	na.	3.69 [1.96–6.5]
Intermittent claudication [60]	282 (28)	na.	6–7 years	1.26 (0.99–1.84)	1.31 (1.06–1.65)	NS	RR: 0.97 [0.78–1.21]

Table 3  
 Prospective cohort studies on the association between Von Willebrand Factor and ischemic stroke.

Study	N	Mean follow-up time	VWF level (IU/ml) in cases	VWF level (IU/ml) in controls	P-value	Disease endpoint OR (95% CI)
ARIC study [30]	14904	na.	White men: 1.22 ± 2 Black men: 1.34 ± 4 White women: 1.15 ± 2 Black women: 1.39 ± 3 1.26 (0.93–1.52)	White men: 1.11 ± 1 Black men: 1.30 ± 2 White women: 1.11 ± 1 Black women: 1.34 ± 1 1.05 (0.78–1.38)	White men: P < 0.05 White women: P < 0.05	Men: NS Women: 1.3, P < 0.05
Edinburgh artery study [4]	1592	5 years	1.36	1.17	NS	RR 1.15 [0.85–1.57]
ARIC study [2]	14713	6–9 years	1.36	1.17	P < 0.0001	1.71 [1.1–2.7]
ARIC study [94]	1393	na.	na.	na.	NS	1.15 [0.97–1.37]
VIP and MONICA study [96]	87	na.	1.49 ± 1.31	1.30 ± 0.87	na.	1.01 [0.61–1.67]
Caerphilly study [51]	2223	13.4 years	na.	na.	na.	HR 0.97 [0.61–1.56]
Edinburgh artery study [25]	1592	17 years	1.17 (0.87–1.57)	1.05 (0.78–1.37)	P < 0.01	HR 1.33 [1.02–1.74]
*three City study (3C) [53]	1254	4 years	1.34 (1.09–1.58)	1.31 (1.09–1.58)	P = 0.469	HR 1.06 [0.49–2.28]
RIC study [93]	464	na.	1.48 (1.30–1.69)	1.33 (1.07–1.47)	P = 0.01	1.9 [1.0–3.4]
otterdam Study [95]	6250	4 years	na.	na.	na.	HR 1.10 [0.95–1.26]
ritish regional heart study [92]	3358	9 years	1.50 ± 0.45	1.37 ± 0.51	P < 0.0001	1.18 [1.02–1.38]

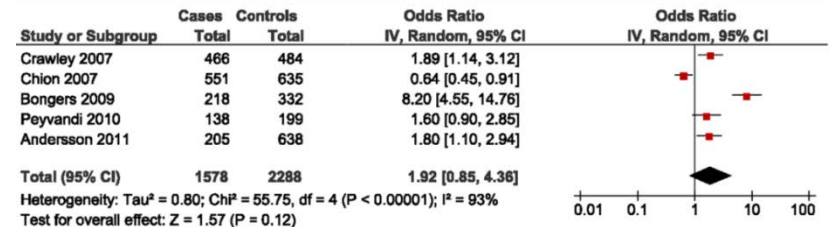
# ADAMTS13 and coronary heart disease

- 8 case-control studies have been performed
- 4 showed a significant association between low levels of ADAMTS13 and risk of MI or CHD
- Others did not find a significant difference in ADAMTS13 levels between MI patients and controls
- meta-analysis of all studies which included cases with a first MI or CHD (N= 1578)
- not significant association between ADAMTS13 levels and myocardial infarction or coronary heart disease (OR 1.92, 95% CI 0.85–4.36) lack of power to statistical significance
- Individuals with high VWF levels and low ADAMTS13 levels confer the highest risk of arterial thrombosis suggests that ADAMTS13 and VWF are independent risk factors.

**Table 2**  
Case-control studies on the association between ADAMTS13 and myocardial infarction.

Participants	N total (% cases)	Blood sampling after event	ADAMTS13 assay	ADAMTS13 in cases	ADAMTS13 in controls	P-value	Disease endpoint OR [95% CI]
First ever MI [31]	1186 (46)	6 months	ELISA	101 (40-350)	100 (41-432)	P = 0.99	1.56 [1.10-2.22]
First ever MI or UAP [46]	550 (40)	1-3 months	ELISA activity and antigen	74.5 (50.6-98.2)	97.4 (81.7-111)	P < 0.001	8.2 [4.5-14.7]
First ever MI [32]	337 (41)	0-3 days	ELISA antigen	118 (97-142)	116 (96-140)	P = 0.48	1.6 [0.9-2.9]
First ever MI [33]	843 (24)	23-146 months	ELISA antigen	100	110	n.a.	1.8 [1.1-3.0]
MI [61]	71 (58)	Acute	ELISA antigen, FRETS activity	76.8 ± 27	89.3 ± 27	P = 0.0014	0.006
MI [41]	950 (49)	3-9 months	ELISA	111 ± 35.9	93.6 ± 29	P = 0.36	5.9 × 10 <sup>-4</sup> -0.59 [1]
MI [40]	132 (70)	Admission, 1,3,7,14 days	ELISA antigen	n.a.	112.6 ± 32.6	P < 0.0001	0.53 [0.32-0.88] day 0; 1.92 [0.16-21.9] day 3; 0.06 [0.002-2.12]
MI [42]	56 (46)	At PCI and chronic phase	ELISA activity	51 ± 15	54 ± 19	NS	n.a.
CHD [143]	55 (62)	Several years	ELISA activity	83 (47-113)	91 (42-122)	NS	n.a.
CHD [142]	29 (48)	n.a.	ELISA activity	n.a.	n.a.	P < 0.01	n.a.
CAD [45]	325 (69)	At angiography and 2-14 days	ELISA antigen	73.5 (62.0-88.8)	82.5 (66.5-95.5)	P = 0.008	HR 0.621 [0.412-0.933]

Figure 2. Forest plot of the association between ADAMTS13 and coronary heart disease



# ADAMTS13 and ischemic stroke

- Few studies have been performed on the association between ADAMTS13 levels and ischemic stroke
- 2 found a significant increased risk of ischemic stroke in individuals with low ADAMTS13 levels
- Other 2 had similar risk estimates, but did not reach statistical significance lack of power due to small number of patients
- meta-analysis of these studies, consisting of 616 cases, and showed a clear association between ADAMTS13 and ischemic stroke (OR 2.72, 95% CI 1.52–4.86) ,
- low ADAMTS13 levels are associated with an increased risk of ischemic stroke.

Figure 3. Forest plot of the association between ADAMTS13 and ischemic stroke

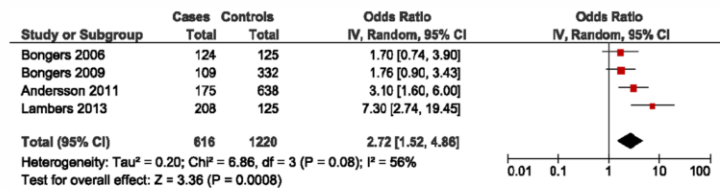


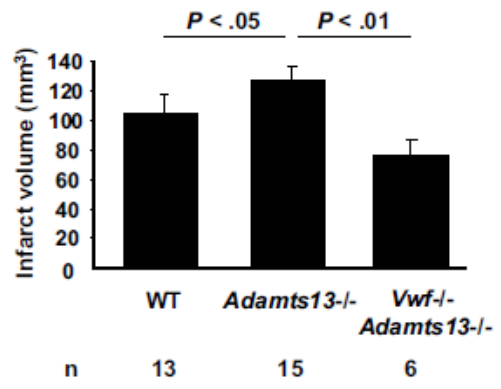
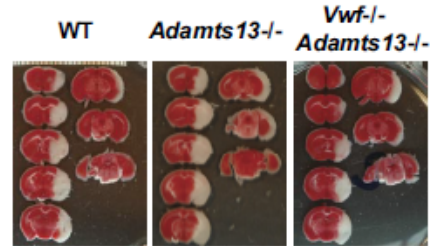
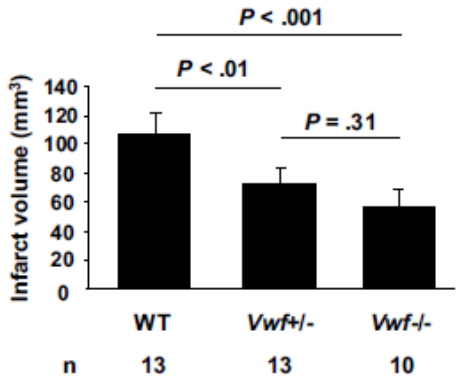
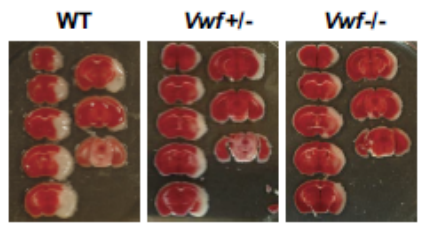
Table 6  
Case-control studies on the association between ADAMTS13 and ischemic stroke.

Participants	N total (% cases)	Blood sampling after event	ADAMTS13 assay	ADAMTS13 level in cases	ADAMTS13 level in controls	P-value	Disease endpoint OR [95% CI]
First ever ischemic stroke [85]	249 (50)	7–14 days	Collagen binding	96 ± 41	103 ± 44	P = 0.23	1.7 [0.7–3.9]
First ever ischemic stroke or TIA [46]	441 (25)	1–3 months	ELISA activity and Antigen	96.4 (70.3–112.2)	109.5 (93–123.8)	P < 0.001	1.76 [0.90–3.44]
First ever ischemic stroke [33]	813 (22)	23–146 months	ELISA antigen	100	110	n.a.	3.1 [1.6–5.8]
Ischemic stroke [144]	333 (62)	6–12 months	ELISA activity	98 (11.1–81)	103 (11.2–91)	P = 0.03	7.30 [2.73–19.5]

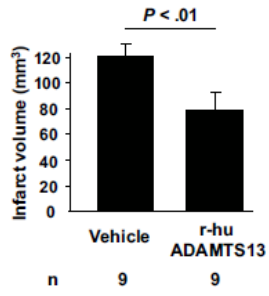
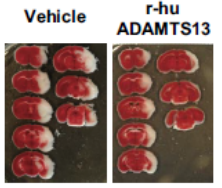
# vonWillebrand factor–cleaving protease ADAMTS13 reduces ischemic brain injury in experimental stroke

Blood. 2009;114:3329-3334

- Deficiency or reduction of VWF reduces infarct volume up to 2-fold after focal cerebral ischemia in mice, showing the importance of VWF in stroke injury.
- In contrast, ADAMTS13 deficiency results in larger infarctions, but only in mice that have VWF
- Importantly, infusion of a high dose of recombinant human ADAMTS13 into a wild-type mouse immediately before reperfusion reduces infarct volume and improves functional outcome without producing cerebral hemorrhage
- recombinant ADAMTS13 did not enhance bleeding

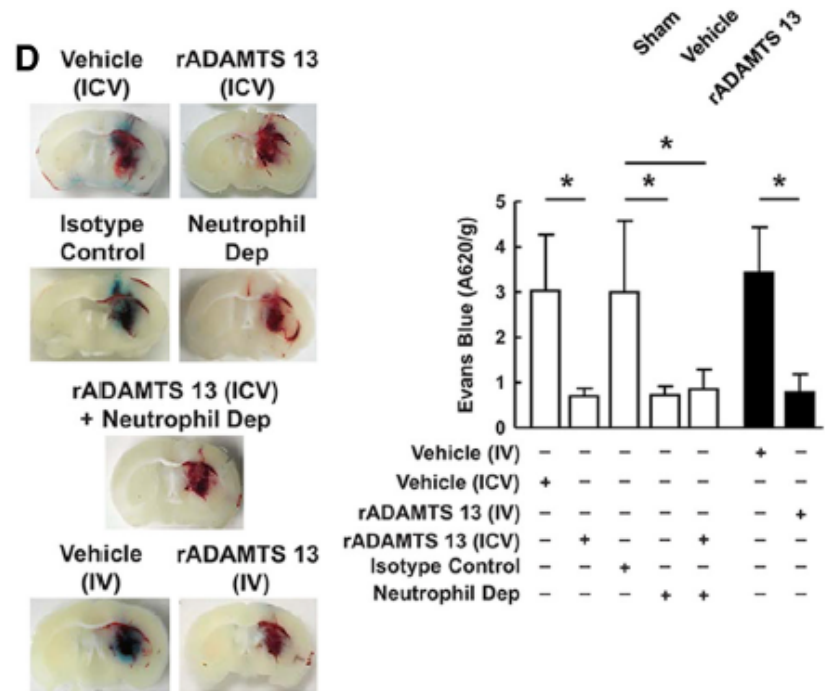


A Derived from HEK 293 cells



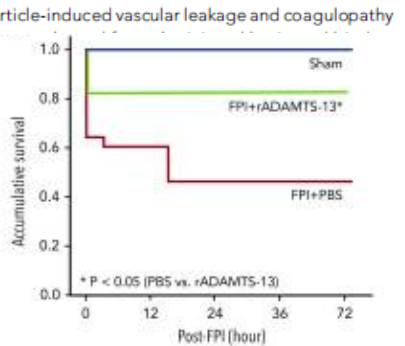
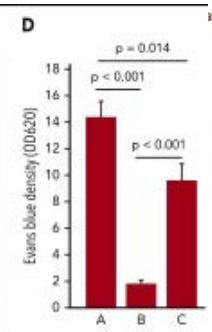
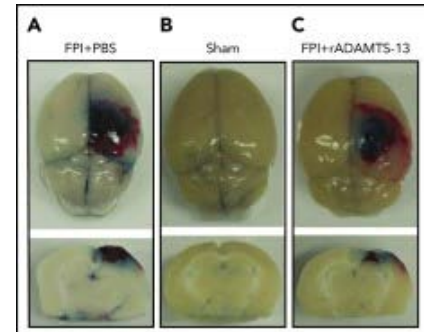
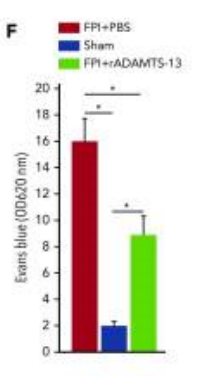
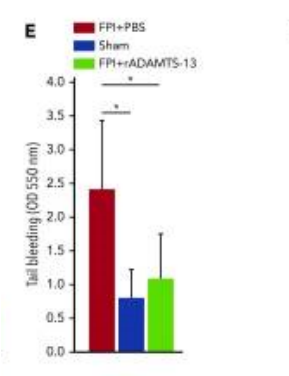
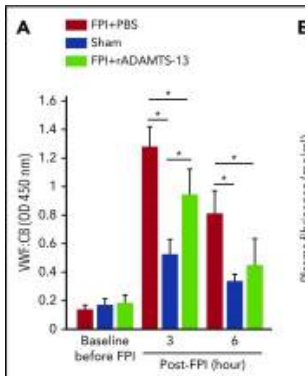
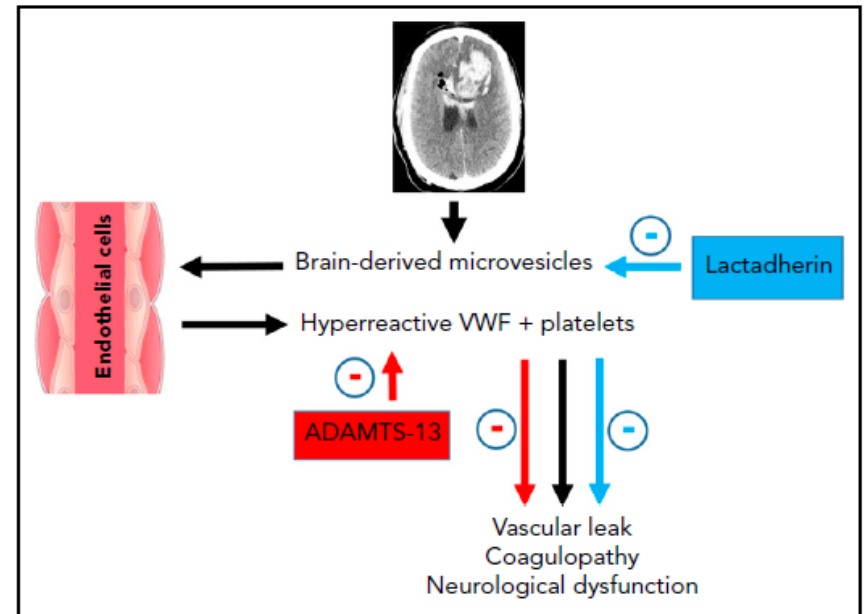
# Recombinant ADAMTS 13 Attenuates Brain Injury After Intracerebral Hemorrhage

- Spontaneous intracerebral hemorrhage (ICH) results from rupture of blood vessels in the brain. It represents  $\approx 10\%$  -  $20\%$  of all strokes and is a devastating clinical condition with a 30-day mortality rate of 30% to 55%.
- no treatment available for improving ICH outcome
- ADAMTS 13 was shown to limit inflammatory responses through its proteolytic effects on von Willebrand factor.
- rADAMTS 13 treatment of mice reduced cerebral edema and hemorrhagic lesion volume and improved neurological functions.
- ***importance of rADAMTS 13 in regulating pathological inflammation and BBB***
- function and suggest that rADAMTS 13 may provide a new therapeutic strategy for ICH.



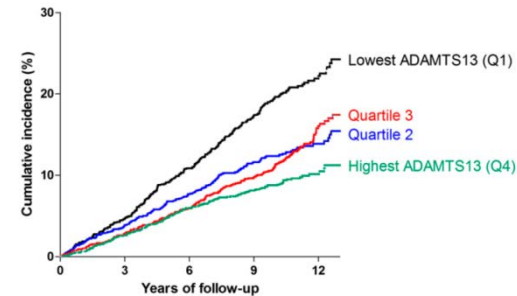
# von Willebrand factor enhances microvesicle-induced vascular leakage and coagulopathy in mice with traumatic brain injury ADAMTS-13 in traumatic brain injury

- In the United States, TBI is a leading cause of death among children and adults
- Each year 1.5million Americans sustain a TBI, with a mortality as high as one-third in patients with severe TBI.
- when coagulopathy accompanies severe TBI, it is an independent predictor of poor prognosis.



# Low ADAMTS13 activity is associated with an increased risk of ischemic stroke

- included 5941 individuals >55 years no history of stroke or transient ischemic attack (TIA) of the Rotterdam Study, a population-based cohort study
- ADAMTS13 activity was measured at inclusion with the FRETs-VWF73 assay and VWF antigen (VWF:Ag) levels by ELISA
- median follow-up time of 10.7 years (56 403 total person-years), 461 participants had a stroke, 306 of which were ischemic.
- After adjustment for cardiovascular risk factors, pts with ADAMTS13 activity in the lowest quartile (< 80.7%) had a higher risk of ischemic stroke (absolute risk, 7.3%) than did those in the reference highest quartile (>102.3%) (absolute risk, 3.8%; hazard ratio, 1.65; 95% confidence interval [CI], 1.16-2.32).
- Adding ADAMTS13 to the model in prediction of ischemic stroke, increased the C-statistic value of the model
- Low ADAMTS13 activity is associated with the risk of ischemic stroke and improves the accuracy of risk predictions for ischemic stroke beyond traditional risk factors.



No. at risk	1486	1304	1079	846	253
Quartile 1	1486	1366	1232	1053	292
Quartile 2	1485	1394	1270	1104	309
Quartile 3	1485	1399	1295	1153	279
Quartile 4	1485	1399	1295	1153	279

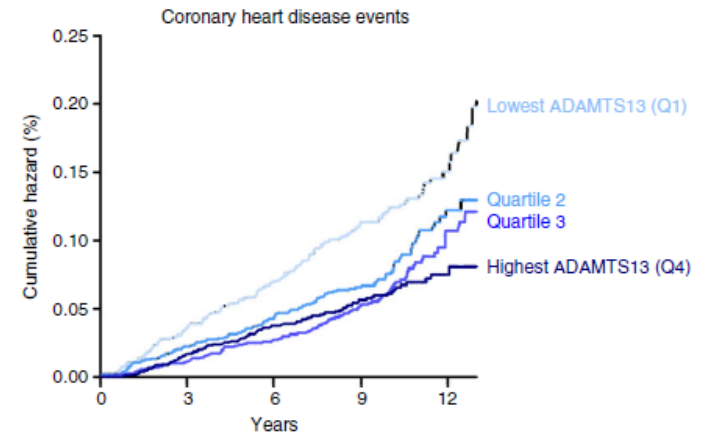
Table 4. Cox proportional hazard regression analysis among ADAMTS13 and VWF and stroke

ADAMTS13 and VWF:Ag level	Number of cases/ Total number at risk	Absolute risk (%)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
<b>All strokes (N = 461)</b>				
VWF < p75 and ADAMTS13 > p25	223/3395	6.6	1 (ref)	1 (ref)
VWF ≥ p75 and ADAMTS13 > p25	79/1055	7.2	0.91 (0.70-1.19)	0.92 (0.71-1.20)
VWF < p75 and ADAMTS13 ≤ p25	101/1032	9.8	1.24 (0.97-1.58)	1.24 (0.97-1.60)
VWF ≥ p75 and ADAMTS13 ≤ p25	61/451	13.5	1.53 (1.14-2.06)	1.49 (1.11-2.01)
<b>Ischemic strokes (N = 306)</b>				
VWF < p75 and ADAMTS13 > p25	153/3395	4.5	1 (ref)	1 (ref)
VWF ≥ p75 and ADAMTS13 > p25	44/1055	4.2	0.83 (0.59-1.16)	0.83 (0.59-1.17)
VWF < p75 and ADAMTS13 ≤ p25	68/1032	6.6	1.31 (0.98-1.76)	1.34 (1.00-1.81)
VWF ≥ p75 and ADAMTS13 ≤ p25	41/451	9.1	1.72 (1.20-2.47)	1.71 (1.19-2.45)
<b>TIA (N = 315)</b>				
VWF < p75 and ADAMTS13 > p25	155/3395	4.6	1 (ref)	1 (ref)
VWF ≥ p75 and ADAMTS13 > p25	58/1055	5.5	1.06 (0.78-1.44)	1.06 (0.78-1.44)
VWF < p75 and ADAMTS13 ≤ p25	72/1032	7.0	1.44 (1.08-1.92)	1.49 (1.11-1.98)
VWF ≥ p75 and ADAMTS13 ≤ p25	29/451	6.4	1.27 (0.84-1.91)	1.29 (0.85-1.95)
<b>Any cerebrovascular event (N = 776)</b>				
VWF < p75 and ADAMTS13 > p25	379/3395	11.2	1 (ref)	1 (ref)
VWF ≥ p75 and ADAMTS13 > p25	134/1055	12.7	0.97 (0.80-1.19)	0.97 (0.80-1.19)
VWF < p75 and ADAMTS13 ≤ p25	173/1032	16.8	1.32 (1.10-1.59)	1.34 (1.11-1.61)
VWF ≥ p75 and ADAMTS13 ≤ p25	90/451	20.0	1.44 (1.13-1.83)	1.43 (1.12-1.82)

Model 1 adjusted for age and sex. Model 2 additionally adjusted for antithrombotic medication, antihypertensive drugs, diabetes mellitus, lipid-reducing agents, BMI, smoking, total cholesterol, HDL cholesterol, systolic blood pressure, and diastolic blood pressure. \*All strokes\* indicates ischemic, hemorrhagic, and unspecified strokes. Any cerebrovascular event indicates all strokes and TIA. ADAMTS13 ≤ 25 percentile represents ≤80.7%, VWF ≥ 75th percentile is ≥1.58 IU/mL.

# Low ADAMTS-13 activity and the risk of coronary heart disease – a prospective cohort study: the Rotterdam Study

- 5688 individuals were included negative for CHD and stroke at baseline.
- Over a median follow-up time of 9.7 years, 456 individuals (8.0%) experienced a cardiovascular event
- 230 of these individuals died as a result of CHD and 226 individuals experienced a myocardial infarction.
- The mean age of all individuals was 68.9 years (8.2) and 59.7% were female
- mean ADAMTS-13 activity was 91.9%
- pts with ADAMTS13 activity in the lowest quartile (< 80.7%) was associated with an increased CHD risk HR 1.42, 95% CI 1.07–1.89) compared with the reference highest quartile (>102.3%)
- There was no relevant correlation between ADAMTS-13 activity and VWF:Ag levels



No. at risk					
Quartile 1	1425	1257	1048	733	134
Quartile 2	1419	1310	1180	906	171
Quartile 3	1421	1342	1234	960	193
Quartile 4	1422	1348	1248	941	167

ADAMTS-13 activity	Mean ADAMTS-13 activity (95% CI)	Number of cases/total number at risk	Model 1 HR (95% CI)	Model 2 HR (95% CI)
CHD event (n = 456)				
Quartile 1	70.5 (70.1–71.0)	156/1425	1.30 (0.98–1.72)	1.42 (1.07–1.89)
Quartile 2	86.4 (86.2–86.5)	116/1419	1.05 (0.79–1.39)	1.10 (0.83–1.47)
Quartile 3	96.6 (96.4–96.7)	99/1421	0.96 (0.72–1.29)	1.00 (0.75–1.34)
Quartile 4	114.3 (113.7–114.9)	85/1422	1 (ref)	1 (ref)
Per SD decrease			1.08 (0.98–1.20)	1.12 (1.01–1.24)

Model 1 adjusted for age and sex. Model 2 additionally adjusted for antithrombotic medication, antihypertensive drugs, diabetes mellitus, lipid

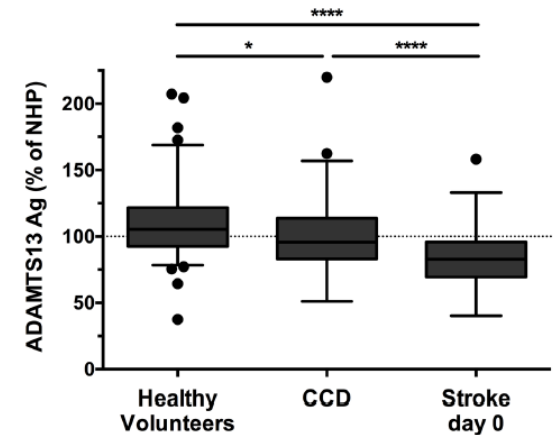
ADAMTS-13 and VWF:Ag level	Number of cases/total number at risk	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
CHD event (n = 453)				
VWF < p75 and ADAMTS-13 > p25	221/3240	1 (ref)	1 (ref)	1 (ref)
VWF ≥ p75 and ADAMTS-13 > p25	77/1015	0.97 (0.74–1.26)	0.98 (0.76–1.28)	0.95 (0.71–1.27)
VWF < p75 and ADAMTS-13 ≤ p25	103/998	1.22 (0.96–1.55)	1.32 (1.03–1.68)	1.40 (1.08–1.81)
VWF ≥ p75 and ADAMTS-13 ≤ p25	52/425	1.41 (1.03–1.93)	1.43 (1.04–1.96)	1.31 (0.92–1.87)

Model 1 adjusted for age and sex. Model 2 additionally adjusted for antithrombotic agents, antihypertensive drugs, diabetes mellitus, lipid reducing agents, smoking, total cholesterol, HDL cholesterol and systolic blood pressure. Model 3 additionally adjusted for blood group. CI, confidence interval.

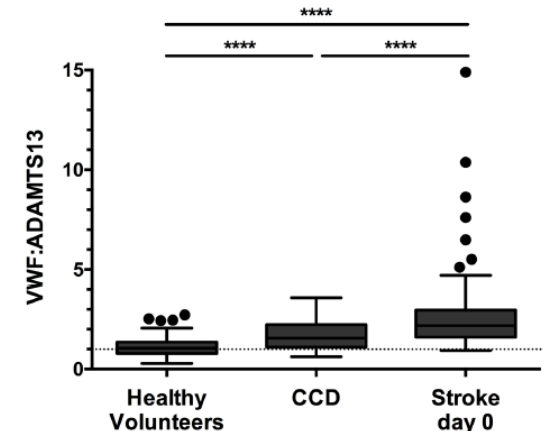
# Reduced ADAMTS13 levels in patients with acute and chronic cerebrovascular disease.

- Correlation with ADAMTS13 levels
- ADAMTS13 in 85 healthy volunteers (HV), 104 patients with acute ischemic stroke and 112 patients with a chronic cerebrovascular disease (CCD)
- ADAMTS13 antigen levels measured by ELISA
- ADAMTS13 levels were significantly lower in acute ischemic stroke patients ( $82.6 \pm 21.0\%$ ) compared with HV ( $110.6 \pm 26.9\%$ ). CCD patients ( $99.6 \pm 24.5\%$ ) had lower ADAMTS13 with HV
- assessing the VWF:ADAMTS13 revealed greater difference between stroke patients ( $2.7 \pm 1.9$ ), HV ( $1.1 \pm 0.5$ ) and CCD patients ( $1.7 \pm 0.7$ )
- In conclusion, both in acute and chronic cerebrovascular disease patients, ADAMTS13 levels were significantly decreased, with the lowest ADAMTS13 levels found in acute stroke patients.

A



B



Denorme F, et al. (2017)

PLoS ONE 12

(6): e0179258. <https://doi.org/10.1371/journal.pone.0179258>

pone.0179258

# RATIO OF VON WILLEBRAND FACTOR PROPEPTIDE TO ADAMTS13 IS ASSOCIATED WITH SEVERITY OF SEPSIS

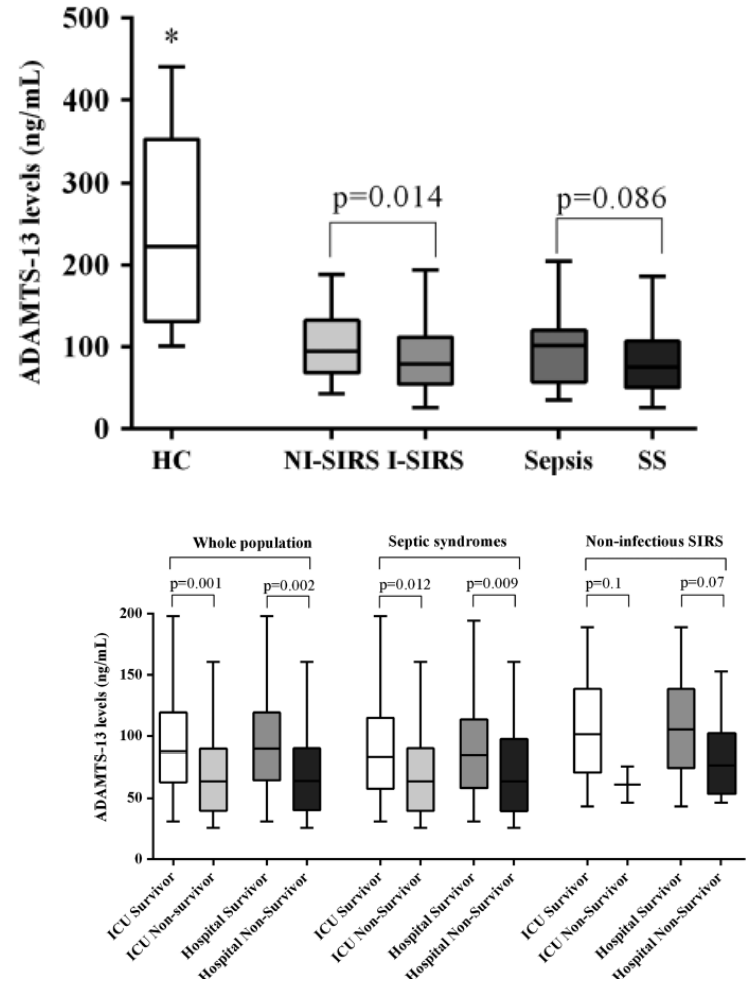
- An imbalance between ULVWF secretion and ADAMTS13 level occurs in sepsis and may cause multiple organ dysfunction.
- Study the association between the VWF-propeptide (VWF-pp)/ADAMTS13 ratio and disease severity in patients with severe sepsis or septic shock.

Variables	Control subjects	Patients with severe sepsis or septic shock			
		Day			
		1	3	5	7
VWF, %	96 ± 14	212 ± 86	228 ± 85	240 ± 85	252 ± 112
VWF-pp, %	96 ± 16	294 ± 154	240 ± 115 <sup>†</sup>	219 ± 117	228 ± 162
ADAMTS13, %					
All patients	100 ± 10	25 ± 8.5 <sup>‡</sup>	30 ± 9 <sup>‡</sup>	33 ± 11 <sup>‡</sup>	33 ± 11
Survivors	NA	27 ± 8.6	31 ± 8.7	35 ± 9.4	36 ± 10
Nonsurvivors	NA	19 ± 5.4	27 ± 8.2	25 ± 10	24 ± 9.4
<i>P</i>	NA	0.03 <sup>§</sup>	NS	0.03 <sup>§</sup>	0.02 <sup>§</sup>
VWF-pp/ADAMTS13 ratio	0.97 ± 0.18	12.9 ± 7.2 <sup>  </sup>	8.9 ± 5.1 <sup>  </sup>	7.7 ± 6.0	7.9 ± 7.1
IL-6, <sup>  </sup> pg/mL	<2.4	1,220 (362–3,610)	206 (58–1,050)	115 (29–338)	75 (20–446)
TNF α (pg/mL)**	<1.8	5.8 (3.3–21.3)	3.4 (2.4–5.8)	2.5 (1.2–4.0)	2.0 (1.4–3.3)

- 27 patients with severe sepsis or septic shock and platelet count less than 120 000/μL, we measured plasma VWF, VWF-pp, and ADAMTS13 levels on hospital days 1, 3, 5, and 7.
- The VWF-pp/ADAMTS13 ratio was increased greater than 12-fold in patients with severe sepsis or septic shock on day 1 and remained markedly high on days 3, 5, and 7 compared with normal control subjects.
- The VWF-pp/ADAMTS13 ratio significantly correlated with APACHE II score on days 1 and 5 SOFA score on days 1, 3, and 5 tumor necrosis factor α level on days 1, 3, 5, and 7 and creatinine level on days 1, 5, and 7.

# ADAMTS-13 IN CRITICALLY ILL PATIENTS WITH SEPTIC SYNDROMES AND NONINFECTIOUS SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

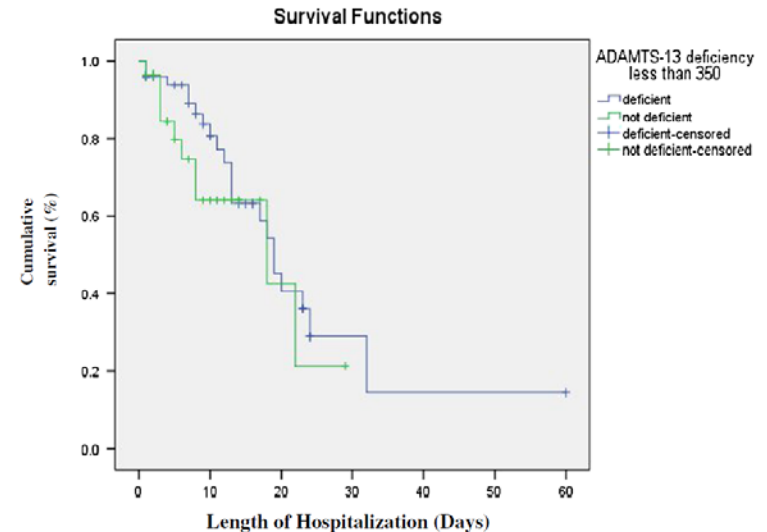
- Decreased ADAMTS-13 and role in different septic syndromes and other causes of systemic inflammatory response syndrome (SIRS)
- aims of this study were to assess ADAMTS-13 levels in patients with septic syndromes or noninfectious SIRS and their association with morbidity and mortality.
- 178 patients admitted to the medical intensive care unit presenting either septic syndromes or noninfectious SIRS.
- ADAMTS-13 Results: Patients with septic syndromes showed significantly lower levels of ADAMTS-13 compared with those with noninfectious SIRS (P = 0.014).
- Patients with severe sepsis or septic shock presented lower levels than those of patients with sepsis (P = 0.086).
- A significant negative correlation between ADAMTS-13 and SOFA & APACHE II at admission in the septic pts.
- Patients who died had significantly lower levels of ADAMTS-13 compared with survivors, especially those with septic syndromes.



# Deficiency of ADAMTS-13 in pediatric patients with severe sepsis and impact on in-hospital mortality

- 80 patients were enrolled in the study.
- median age was 3.1 years (Range: 0.1-15 years)
- ADAMTS-13 deficiency with levels less than 350 ng/dl was found in 65% patients.
- In patients with ADAMTS-13 deficiency, 75.6% had low platelets of less than  $150 \times 10^9/L$ .
- In-hospital mortality was 42.3% and 35.7% in ADAMTS-13 deficient and non-deficient group, respectively.
- The mean duration of hospitalization was 12.4 days in patients with ADAMTS-13 deficiency, while it was 8.8 - days in the non-deficient group. The difference was not statistically significant.
- Conclusion: Majority of the pediatric patients admitted to hospital with severe sepsis exhibit ADAMTS-13 deficiency.
- ADAMTS-13 deficiency might play a role in sepsis-induced thrombocytopenia. More studies are needed to evaluate the role of ADAMTS-13 deficiency on in-hospital mortality.

Karim et al. BMC Pediatrics 2013, 13:44



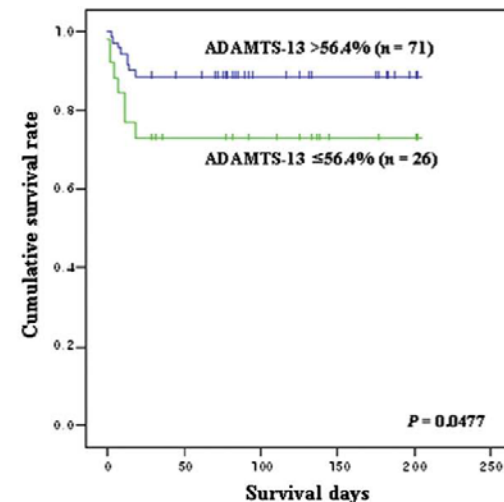
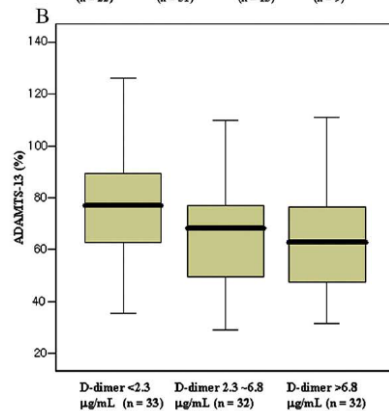
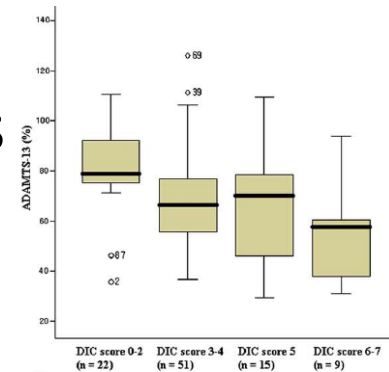
| Cumulative survival of patients with and without ADAMTS-13 Deficiency.

# THE ROLE OF ADAMTS-13 IN THE COAGULOPATHY OF SEPSIS

- Sepsis is another clinical condition in which thrombotic microangiopathy may occur, and this is often associated with decreased levels of ADAMTS-13.
- thrombotic microangiopathy, associated with sepsis is caused by enhanced platelet-vessel wall interaction crucial factor in the pathogenesis of this enhanced platelet-vessel wall interaction is thought to be the release of (ultra-large) von Willebrand factor multimers
- Hypothetically, the inflammation-mediated massive release of von Willebrand factor from the endothelium consumes and depletes the available concentration of ADAMTS-13
- Other factors that may contribute to the reduction in plasma activity of ADAMTS-13 in patients with sepsis are proteolytic cleavage by neutrophil elastase, thrombin, or plasmin (which are all being generated during sepsis), and inhibition of the metalloprotease by pro-inflammatory cytokines, such as interleukin (IL)-6.
- Up to one third of patients with sepsis have ADAMTS-13 levels that are <50% of normal
- Patients with ADAMTS-13 plasma concentrations  $\leq 50\%$  had an approximate 10% higher risk of death compared with patients who present with no or only mild reduction in ADAMTS-13 levels.
- A strong association is reported between the magnitude of decrease in ADAMTS-13 levels in patients with sepsis and an adverse outcome. Significantly lower ADAMTS-13 levels are seen at the time of admission in eventual non-survivors
- 50% lower survival rate in patients (mortality 59%) with septic shock and ADAMTS-13 levels <30%, compared with patients having higher levels of ADAMTS-13 (mortality 28%)
- The predictive value of ADAMTS-13 deficiency for mortality was as powerful as APACHE II or similar risk Scores
- plasma exchange evidence base in sepsis is inconclusive

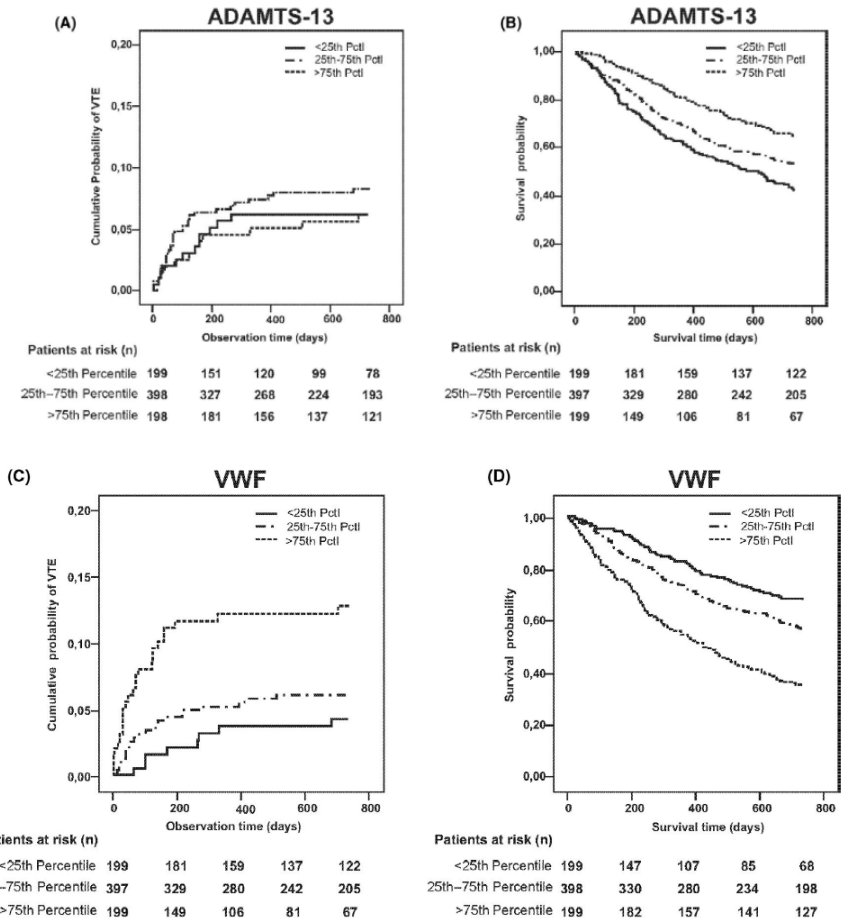
# Correlation between plasma activity of ADAMTS-13 and coagulopathy, and prognosis in disseminated intravascular coagulation

- DIC widespread activation of intravascular coagulation accompanied with endothelial activation results in release of ULvWF
- ADAMTS-13 may be consumed through the ongoing cleavage of ULvWF, resulting in a secondary deficiency of ADAMTS-13 in DIC.
- ADAMTS-13 activity was tested in 97 patients who were clinically suspected to have DIC
- ADAMTS-13 activity gradually decreased based on the DIC score and D-dimer levels and was correlated with the ATIII level
- There were no correlation between ADAMTS-13 activity and neutrophil CD64 expression as a neutrophil activation marker
- Patients with a low activity of ADAMTS-13 ( $\leq 56.4\%$ ) had a poor survival rate compared to patients with a high activity of ADAMTS-13.
- ADAMTS-13 activity is strongly correlated with the severity of coagulopathy and hospital mortality.
- ADAMTS-13 may serve as a diagnostic and prognostic marker of DIC

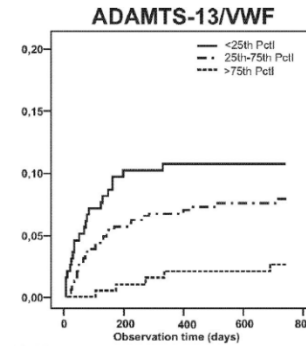


# The role of ADAMTS-13 and von Willebrand factor in cancer patients: Results from the Vienna Cancer and Thrombosis Study (CATS)

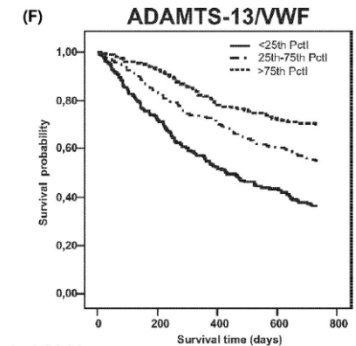
- Objectives: Investigation of the influence of ADAMTS-13 and VWF on the probability of VTE and survival in malignancy.
- 795 patients with various tumor types (364 female/431 male, median age 62 y) were included
- 56 developed VTE / 359 patients died during a median follow-up of 730 d
- The hazard ratio (HR) of VTE per doubling of VWF level was 1.56 ,ADAMTS-13 levels showed no correlation with VTE incidence but with mortality



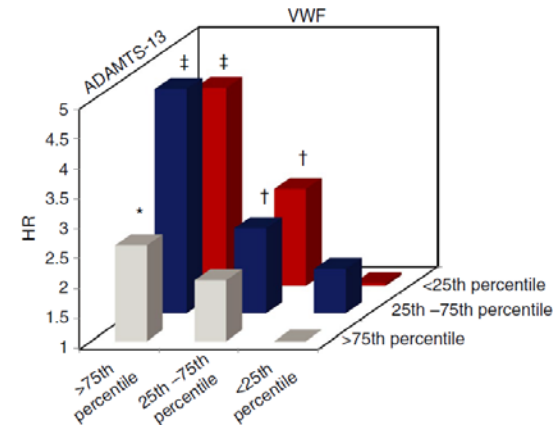
- patients with VWF values above the 75th had 3-fold risk of developing VTE compared to those below the 25th percentile after 2 years.
- For the ADAMTS-13/ VWF this difference was even 4-fold between levels <25<sup>th</sup> percentile and >75th percentile, respectively. ADAMTS-13 does influence the predictive potential of the ratio for cancer-associated VTE, concerning the stratification of low-risk patients.
- A statistically significant difference in survival probability according to values of ADAMTS-13, VWF and the ADAMTS-13/VWF ratio could be found in Kaplan-Meier analysis
- The probability of survival after 2 years in patients with VWF above the 75<sup>th</sup> and below the 25th percentile was 35.0% and 67.7%, respectively.
- The corresponding probabilities in patients with values >75th versus <25th percentile for ADAMTS-13 were 65.3% versus 42.7% and for the ADAMTS-13/VWF ratio 69.4% versus 36.1%, respectively.



isk (n)	<25th Pctl	25th-75th Pctl	>75th Pctl
centile 199	147	107	85
centile 398	330	280	234
centile 199	182	157	141

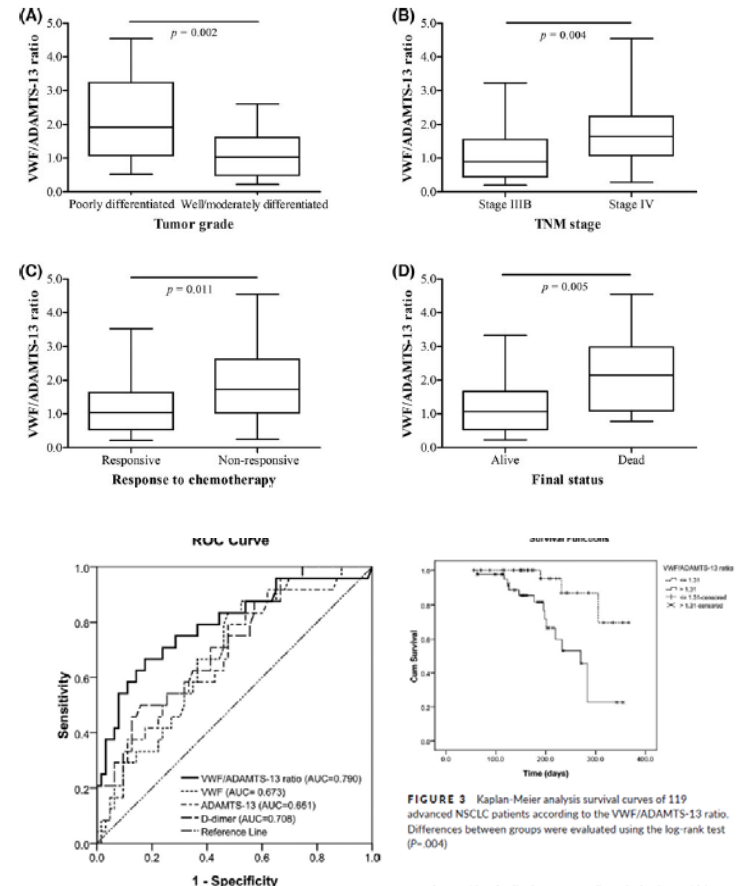


Patients at risk (n)	<25th Percentile	25th-75th Percentile	>75th Percentile
centile 199	181	159	137
centile 398	329	280	242
centile 199	149	106	81



# Increased von Willebrand factor over decreased ADAMTS-13 activity is associated with poor prognosis in patients with advanced non-small-cell lung cancer

- 119 patients with advanced NSCLC and 102 healthy controls.
- All patients were followed up to determine the predictive value of elevated VWF, VWF/ADAMTS-13 ratio, and reduced ADAMTS-13 for prognosis of advanced NSCLC
- Significantly correlated with the stage and grade of advanced NSCLC and the final status of disease ( $P < .05$ ).
- *VWF levels and the VWF/ADAMTS-13* were also associated with response to chemotherapy ( $P < .05$ ).
- *VWF/ADAMTS-13* ratio as significant independent predictors of patient mortality. The area under the curve showed that the *VWF/ADAMTS-13* ratio was more useful than VWF, ADAMTS-13, and D-dimer to predict mortality. Kaplan-Meier analysis showed that a low *WF/ADAMTS-13* ratio was significantly predictive of improved survival ( $P = .004$ ).



**FIGURE 3** Kaplan-Meier analysis survival curves of 119 advanced NSCLC patients according to the VWF/ADAMTS-13 ratio. Differences between groups were evaluated using the log-rank test ( $P = 0.004$ ).

# Plasma ADAMTS-13 activity in proliferative lupus nephritis: a large cohort study from China

- 163 pts class III and IV lupus nephritis patients confirmed by biopsy examinations and 98 normal controls
- Plasma ADAMTS-13 activity in lupus nephritis patients was significantly lower than that in normal controls ( $p > 0.005$ ).
- The plasma level of vWF was significantly higher in the lupus nephritis group than in normal controls ( $p = 0.025$ ).
- Plasma ADAMTS-13 activity was negatively correlated with the level of serum creatinine and proteinuria
- Plasma ADAMTS-13 activity was negatively associated with total pathological AI scores and acute renal vascular lesions ( $p < 0.001$ ).
- No association was found between level of vWF and plasma ADAMTS-13 activity
- Low level of ADAMTS-13 activity was a risk factor for renal outcomes

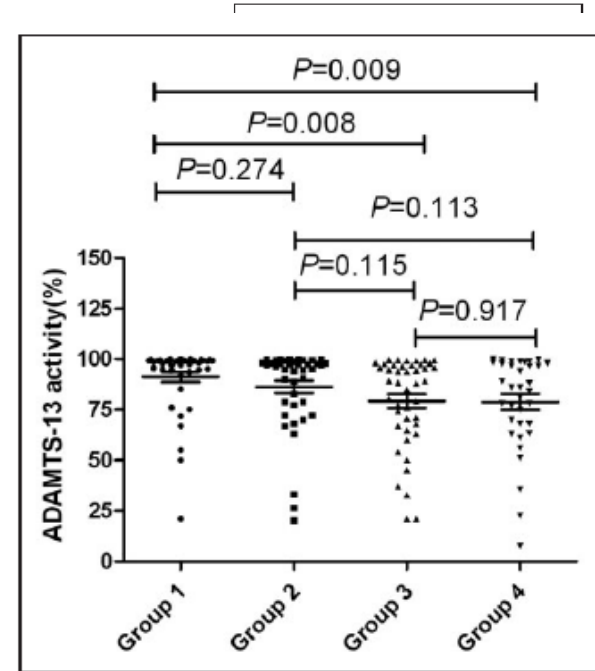


Figure 4 Plasma ADAMTS-13 activity in four groups of lupus nephritis patients with different SLEDAI scores based on quartile interval. Horizontal solid lines indicate mean values SD values for each group. Group 1, patients with SLEDAI score no more than 15; Group 2, patients with SLEDAI score 16–18; Group 3, patients with SLEDAI score 19–22; Group 4, patients with SLEDAI score over 23. ADAMTS-13: a disintegrin-like and metalloprotease with thrombospondin type 1 motif; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

# von Willebrand Factor and Venous Thromboembolism

- VWF can mediate platelet adhesion on endothelium and subendothelium at shear rates as low as 50 and 200/s characteristic of veins and venules, respectively.
- in vivo animal experimental models: (1) injury induced vein thrombosis and (2) flow restriction-induced vein thrombosis multiple experiments implicate VWF in venous thrombosis
- Chauhan et al described impaired thrombus formation in VWF-knock out mice models of ferric chloride-injured veins and venules. In their model (shear rates <150/s), mice showed significantly reduced platelet adhesion to subendothelium, resulting in formation of small, nonocclusive thrombi (no vessels fully occluded) compared to wild-type mice
- In humans histopathological findings in humans have clearly demonstrated that venous thrombi are not only rich in erythrocytes and fibrin but also in platelets and VWF, thus supporting its involvement in VTE
- In a recent analysis of the Multiple Environmental and Genetic Assessment of risk factor for venous thrombosis (MEGA) study, elevated plasma levels of VWF (>80th percentile of control population) in outpatients were found to be associated with a 4-fold increase in the risk of VTE, reaching a risk of 88-fold increase in combination with immobilization and a major illness.
- Karakaya et al also investigated the role VWF and ADAMTS-13 in 30 patients with a history of VTE, who had the same blood group (blood type O). Compared with a control group, patients with previous VTE presented significantly higher mean VWF levels (1,750 vs. 950;  $p < 0.0001$ ) and a lower median ADAMTS-13 level (280 ng/mL vs. 665 ng/mL;  $p < 0.0001$ ), thus suggesting a possible involvement of VWF/ADAMTS-13 axis in the pathological process.
- Despite the data mentioned earlier, the exact causal role of VWF in VTE still remains to be firmly established.

# The ADAMTS13–VWF axis is dysregulated in chronic thromboembolic pulmonary hypertension(CTEPH)

- Chronic thromboembolic pulmonary hypertension (CTEPH) is an important consequence of PE 3% of pts
- ADAMTS13–von Willebrand factor (VWF) axis in CTEPH, including its relationship with disease severity, inflammation, ABO groups
- ADAMTS13 and VWF plasma antigen levels were measured in patients with CTEPH (n=208), chronic thromboembolic disease without pulmonary hypertension (CTED) (n=35), resolved PE (n=28), idiopathic pulmonary arterial hypertension (n=30) and healthy controls (n=68).
- In summary, we report that the ADAMTS13–VWF axis is dysregulated in CTEPH and this is unrelated to pulmonary hypertension, disease severity or systemic inflammation. This implicates the ADAMTS13– VWF axis in CTEPH pathogenesis

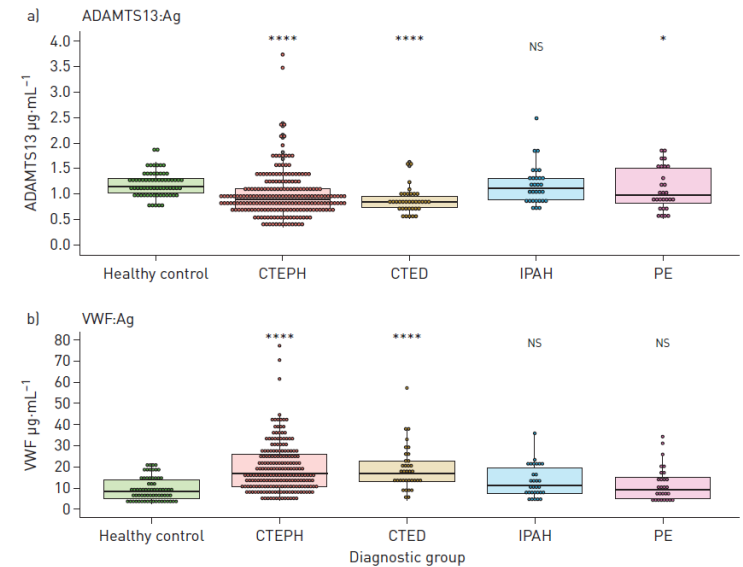


FIGURE 1 a) ADAMTS13 and b) von Willebrand factor (VWF) antigen (Ag) levels by diagnostic group. Dunn's test with false discovery rate adjustment was used to calculate p-values. Healthy control, n=68; chronic thromboembolic pulmonary hypertension (CTEPH), n=208; chronic thromboembolic disease (CTED), n=35; idiopathic pulmonary arterial hypertension (IPAH), n=28; pulmonary embolism (PE), n=28. \*: p<0.05; \*\*: p<0.01; \*\*\*: p<0.001; \*\*\*\*: p<0.0001; ns: nonsignificant.

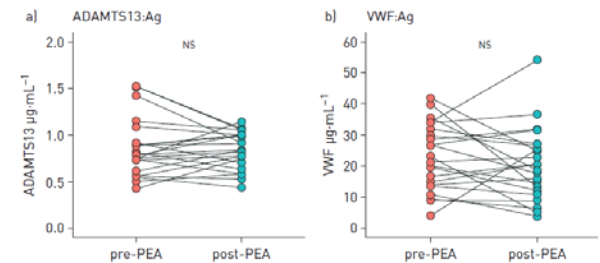


FIGURE 2 a) ADAMTS13 and b) von Willebrand factor (VWF) antigen (Ag) levels pre- and post-pulmonary endarterectomy (PEA) (n=22). Wilcoxon signed-rank test was used to calculate p-values. ns: nonsignificant.

# conclusions

- Growing clinical and experimental evidence suggests the importance of the VWF–ADAMTS-13 axis not only in hemostasis, bleeding disorders, and TTP, but also in cardiovascular disease and other diseases.
- The improved knowledge of the dynamics of interactions may first impact on the understanding of these complex diseases, and then also offer the potential for improved interventions.
- A Phase 3, Randomized, Controlled Study of Prophylactic and On-demand Treatment of cTTP With BAX 930 (rADAMTS13)

