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Prothrombotic genotypes and risk of venous thromboembolism in cancer

John-Bjarne Hansen MD PhD

K.G. Jebsen Thrombosis Research and Expertise Center (TREC)

UiT – The Arctic University of Norway

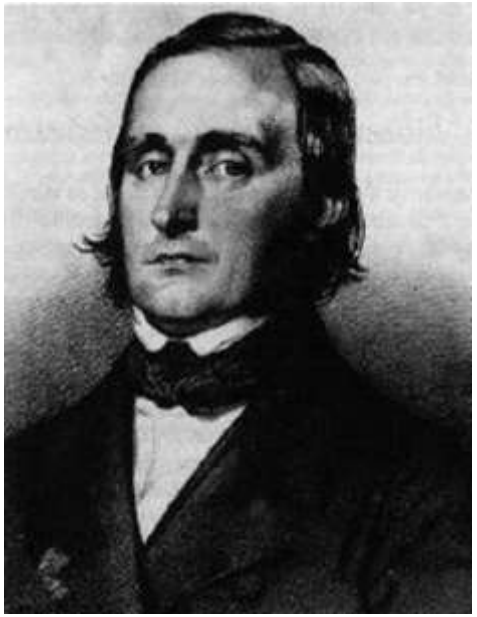
Tromsø, Norway

STIFTELSEN KGJ

UNIVERSITY OF TROMSØ

Cancer-related VTE

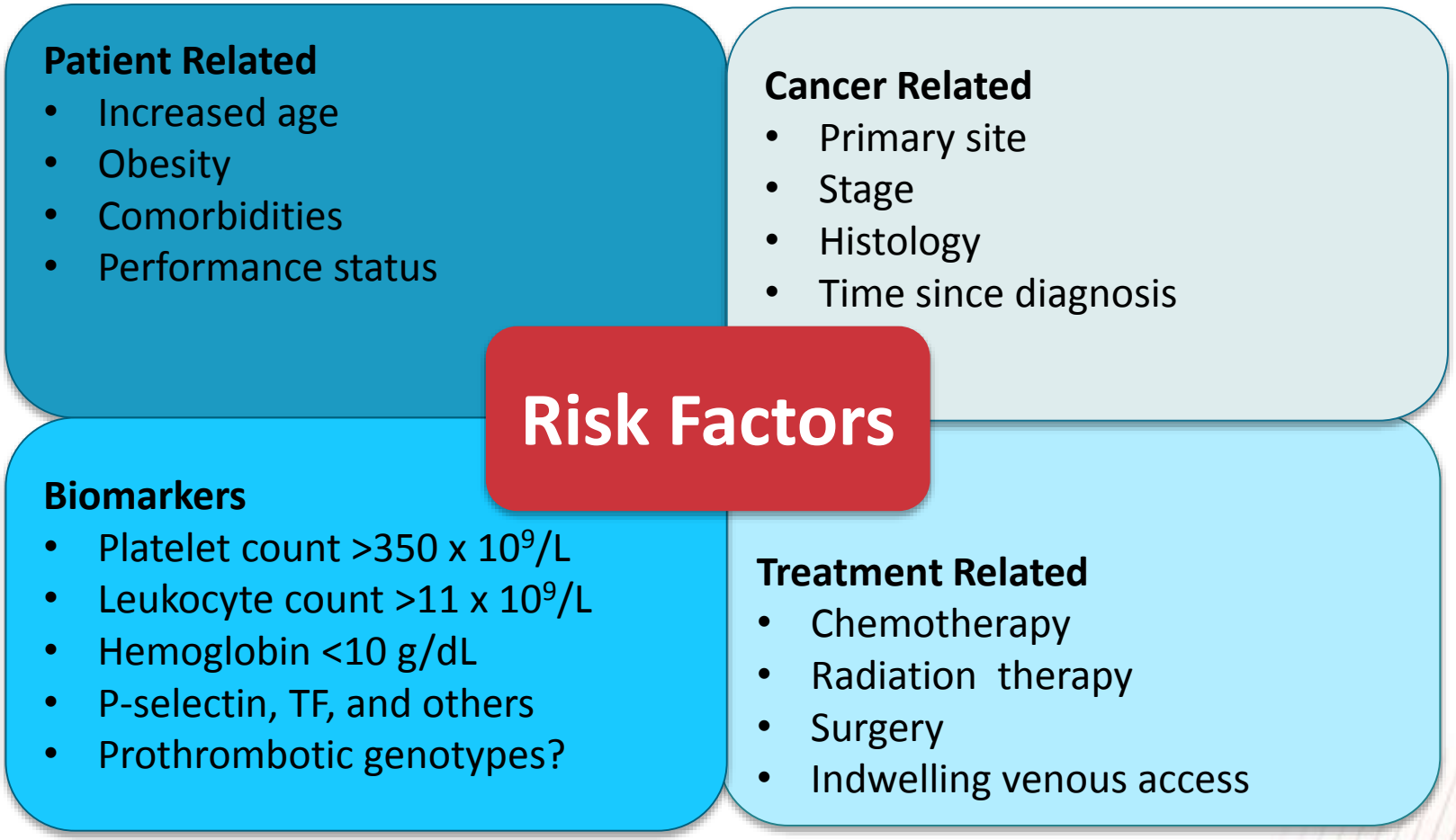
- **Of all cases of VTE:**
  - 20 to 25% occur in cancer patients[1]
  - Incidence of VTE in cancer patients is increasing[2]
- **Of all cancer patients:**[3]
  - 15% will have a symptomatic VTE during the course of their disease
  - Up to 50% have a VTE at autopsy
- **Compared to patients without cancer:**[3-5]
  - Higher risk of VTE
  - Higher risk of bleeding on anticoagulants
  - Higher risk of death



www.armandtrousseau.wifeo.com

1. Timp et al, *Circulation*, 2013
2. Walker et al, Eur J Cancer, 2013
3. Lee et al, *Circulation*, 2003
4. Khorana, *Thromb Res*, 2010
5. Prandoni et al, *Blood,* 2002

Risk factors for cancer-related VTE



Outline

- **The impact of patient-related risk factors for cancer-related VTE**
- Prothrombotic genotypes and cancer-related VTE
- Conclusions

The Scandinavian Thrombosis and Cancer cohort (STAC)

TROMSØ 4 (1994-1995)

Invited (n): 37558
Participated (n): 27158
Attendance rate: 77%
Age: 25-97 years

HUNT 2 (1995-1997)

Invited (n): 93898
Participated (n): 65237
Attendance rate: 69%
Age: 19-103 years

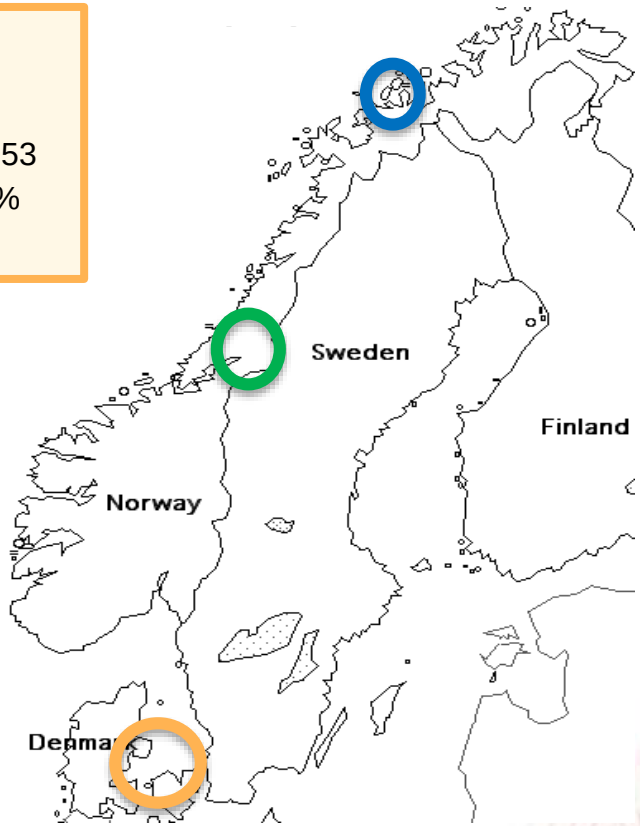
DCH (1993-1997)

Invited (n): 160725
Participated (n): 57053
Attendance rate: 35%
Age: 50-64 years

Excluded prior to merging:
Previous cancer or VTE

STAC COHORT (1993-1997)

Included: 144952
Age: 19-101 years
Followed up to 2007-2012
Cancer diagnoses (n): 19757
VTE events (n): 2444



Jensvoll H et al, Clin Epidemiol 2015;7:401-10

Aims

- To assess the overall- and time-specific risk of VTE in cancer patients recruited from three large population-based cohorts

- To compare the short-term cumulative incidence for each cancer site taking competing risk by death into account

CANCER

CANCER SITES

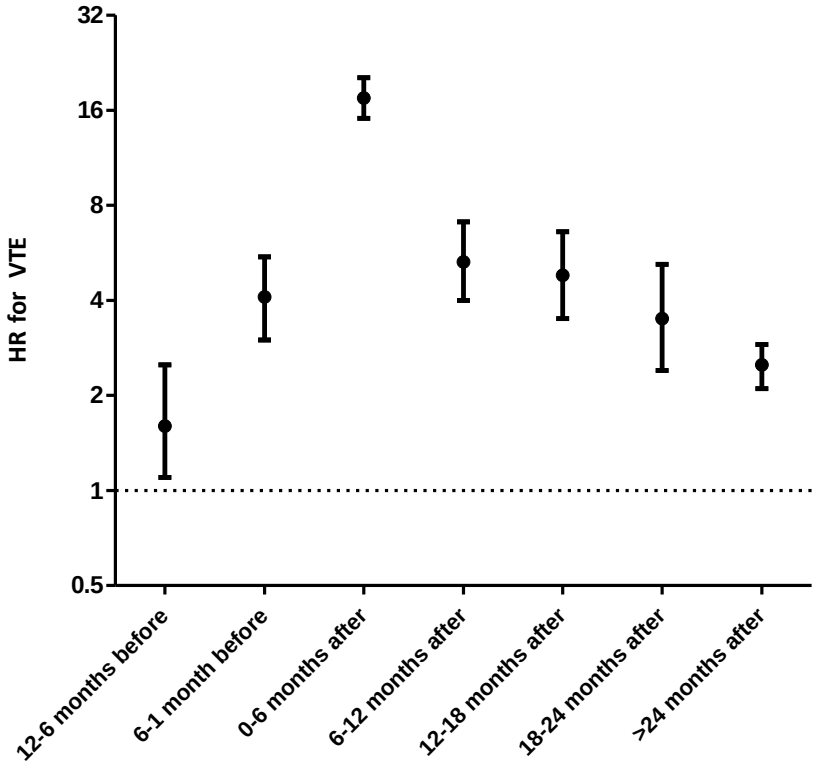
TIME-SPECIFIC

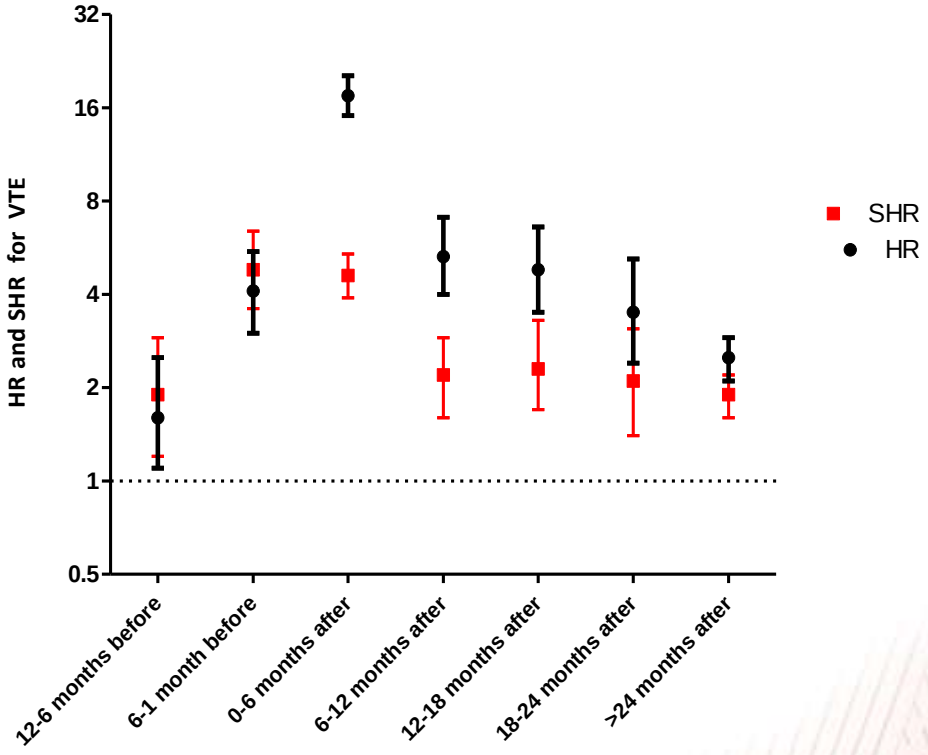
COMPETING RISK BY DEATH

VTE

Blix K et al, J Thromb Haemostas 2018

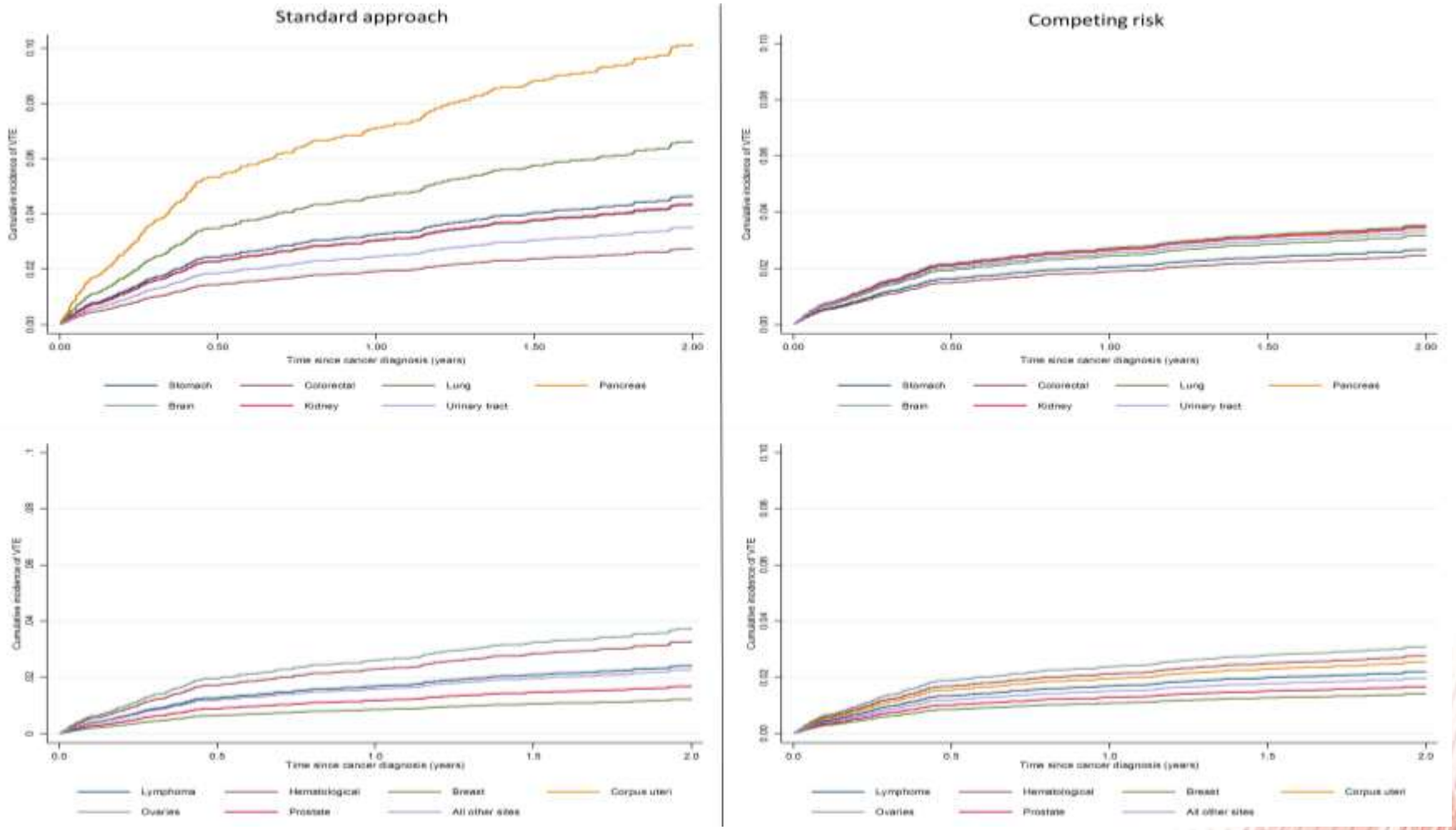
Impact of time since cancer diagnosis and prognosis on risk of VTE





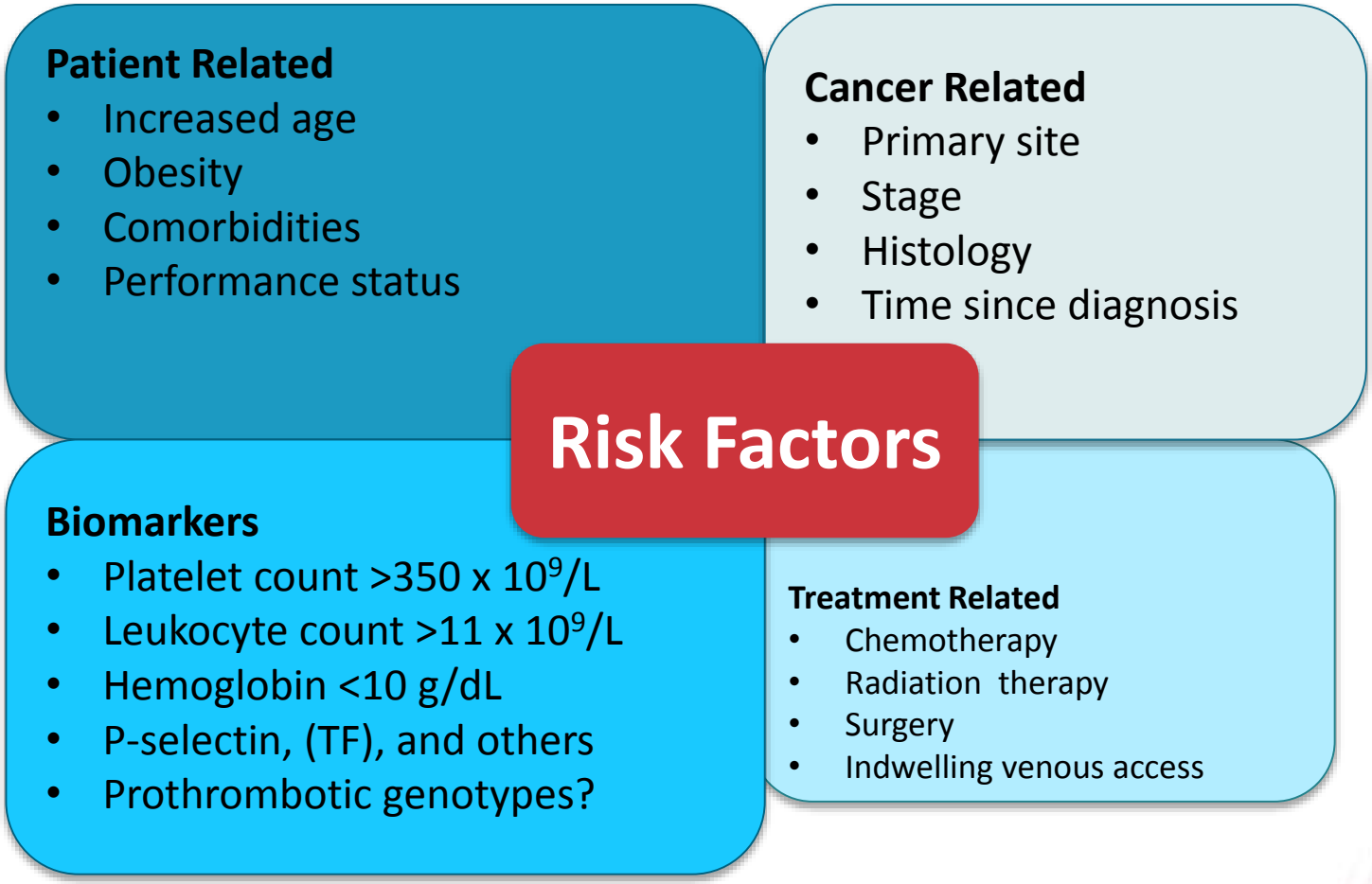
Blix K et al, J Thromb Haemost 2018

Cumulative incidence of VTE across different cancer sites



Blix K et al, J Thromb Haemostas 2018

Risk factors for cancer-related VTE

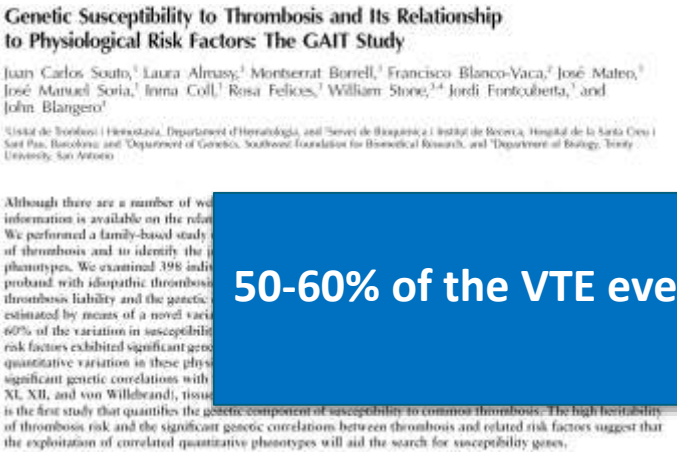


Outline

- The impact of patient-related risk factors for cancer-related VTE
- **Prothrombotic genotypes and cancer-related VTE**
- Conclusions

Heritability of VTE

Family



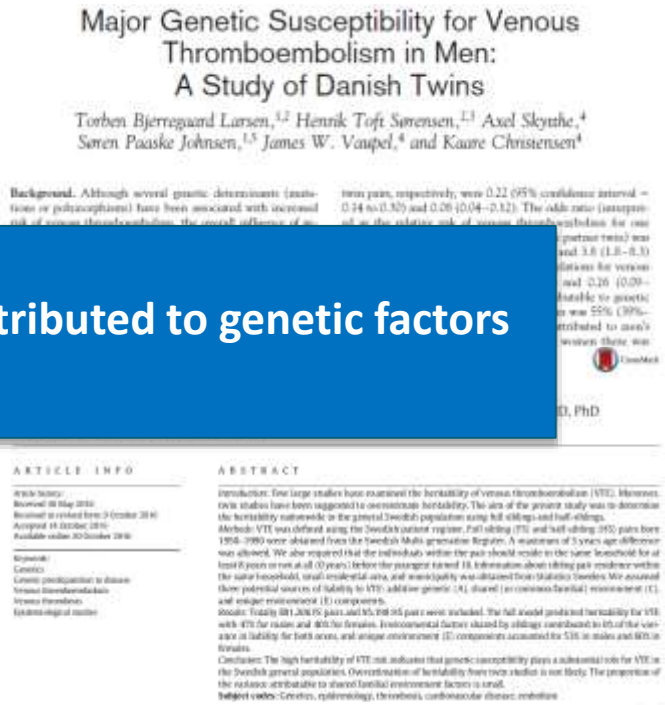
Genetic Susceptibility to Thrombosis and Its Relationship to Physiological Risk Factors: The GAIT Study

Juan Carlos Souto,[1] Laura Almasy,[2] Montserrat Borrell,[3] Francisco Blanco-Vaca,[4] José Mateo,[3] José Manuel Soria,[1] Inma Coll,[1] Rosa Felices,[3] William Stone,[3,4] Jordi Fontcuberta,[1] and John Blangero[2]

[1]Unitat de Trombosi i Hemostasia, Departament d'Hematologia, and [3]Servei de Bioquímica i Institut de Recerca, Hospital de la Santa Creu i Sant Pau, Barcelona; and [2]Department of Genetics, Southwest Foundation for Biomedical Research, and [4]Department of Biology, Trinity University, San Antonio

Although there are a number of wel
information is available on the relat
We performed a family-based study
of thrombosis and to identify the p
phenotypes. We examined 398 indiv
proband with idiopathic thrombosis
thrombosis liability and the genetic
estimated by means of a novel vari
60% of the variation in susceptibilit
risk factors exhibited significant gen
quantitative variation in these phys
significant genetic correlations with
XI, XII, and von Willebrand), tissue
is the first study that quantifies the genetic component of susceptibility to common thrombosis. The high heritability of thrombosis risk and the significant genetic correlations between thrombosis and related risk factors suggest that the exploitation of correlated quantitative phenotypes will aid the search for susceptibility genes.

Twin



Major Genetic Susceptibility for Venous Thromboembolism in Men: A Study of Danish Twins

Torben Bjerregaard Larsen,[1,2] Henrik Toft Sørensen,[2,3] Axel Skytthe,[4] Søren Paaske Johnsen,[1,5] James W. Vaupel,[4] and Kaare Christensen[4]

Background. Although several genetic determinants (mutations or polymorphisms) have been associated with increased risk of venous thromboembolism, the overall influence of ge

twin pairs, respectively, were 0.22 (95% confidence interval = 0.14 to 0.32) and 0.08 (0.04–0.12). The odds ratio (interpretation as the relative risk of venous thromboembolism for one partner twin) was and 3.8 (1.8–8.3) ulations for venous and 0.26 (0.09– table to genetic was 55% (39%– ributed to men's women there was

D, PhD

ARTICLE INFO

ABSTRACT

50-60% of the VTE events is attributed to genetic factors

Souto JC et al, Am J Hum Genet, 2000
Larsen TB et al, Epidemiology, 2003
Zöller B et al, Thromb Res, 2017

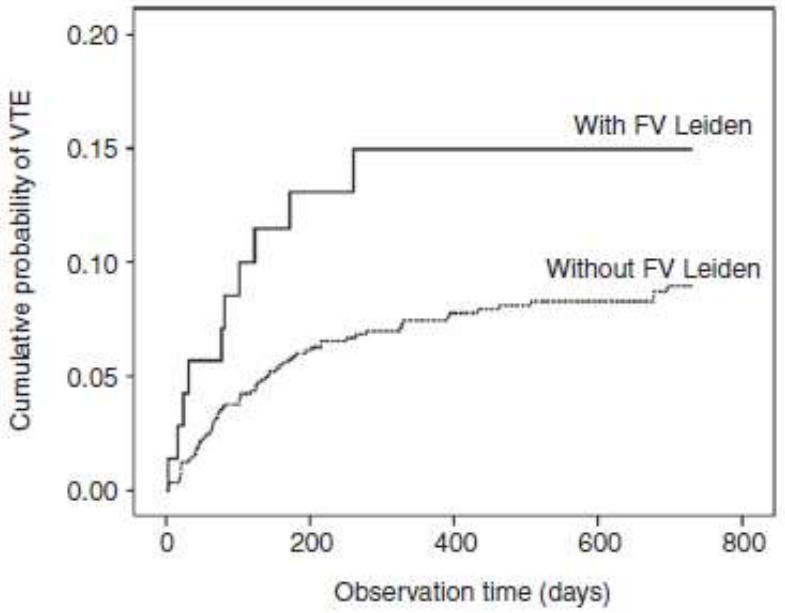
Prothrombotic single nucleotide polymorphisms and VTE risk

Gene	Site	Phenotype	Frequency	VTE OR
Genes associated with VTE identified before GWAS				
F2	rs1799963	VTE	0.02	2.50
F5	rs6025	VTE	0.05	3.00
FGG	rs2066865	VTE	0.25	1.47
ABO	rs8176719	VTE	0.3	1.50
PROC	multiple	VTE	rare	~10
PROS1	multiple	VTE	rare	~10
SERPINC1	multiple	VTE	rare	~10
Novel SNPs associated with VTE identified by GWAS				
VWF	rs1063856	Increased vWF	0.37	1.15
STXBP5	rs1039084	Increased vWF	0.46	1.11
GP6	rs1613662	Increased platelet function	0.82	1.15
F11	rs2289252	Increased FXI	0.41	1.35
F11	rs2036914	Increased FXI	0.52	1.35
C4BPB/C4BPA	rs3813948	Increased C4BP	0.08	1.18
KNG1	rs710446	Increased aPTT	0.45	1.20
SERPINC1	rs2227589	Decreased antithrombin	0.10	1.29
TSPAN15	rs78707713	Unknown	0.88	1.28

Modified from Morange PE et al, Thromb Haemost, 2015

FV Leiden and cancer-related VTE – The Vienna Cancer and Thrombosis Study (CATS)

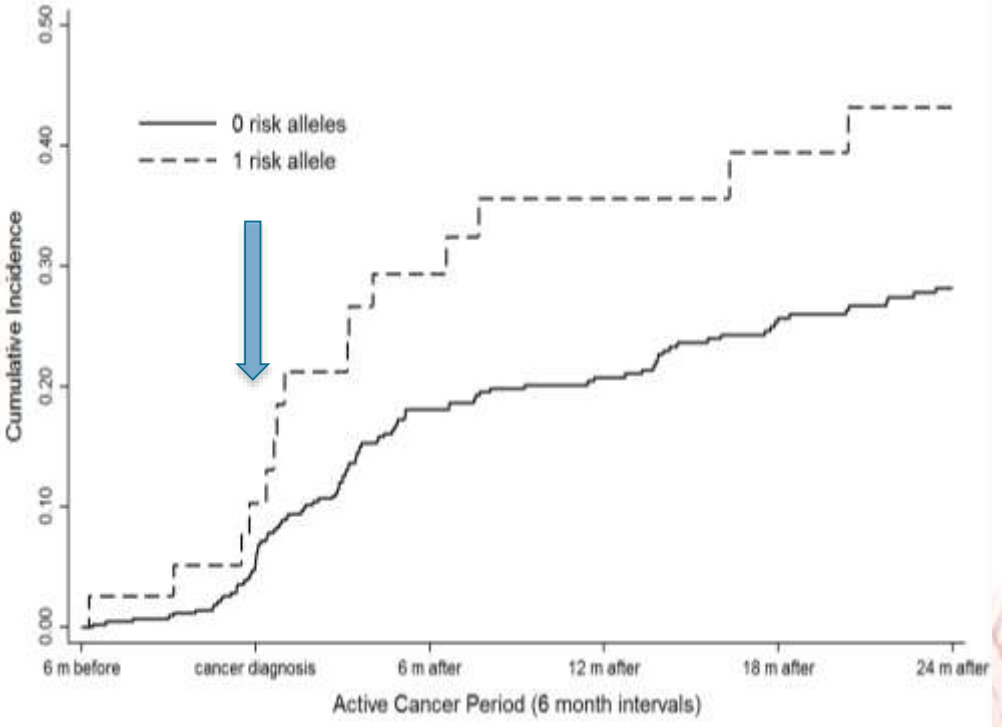
- Cohort of 982 patients with cancer
- Followed for a maximum of 2 years
- 79 VTEs
- 2-fold increased risk of VTE in those with FVL
- The risk was particularly high during the first 3 months after cancer diagnosis



Pabinger I et al, J Thromb Haemost 2015;13:17-22

FV Leiden and cancer-related VTE – The Tromsø Study

- Case-cohort study
- 609 VTE patients and a sub-cohort of 1691 individuals
- Those with FVL had a 1.9-fold higher risk of cancer-related VTE
- The risk was particularly high during the first 6 months after cancer diagnosis



Gran et al. Haematologica 2016;101:1046-1053

Risk of VTE according to FV Leiden and cancer status

Cancer status	Risk alleles	n	VTE HR (95% CI)	n	DVT HR (95% CI)	n	PE HR (95% CI)
No cancer	0	374	1.0	198	1.0	176	1.0
	1	63	2.1 (1.6-2.7)	47	2.9 (2.1-4.0)	16	1.5 (0.7-1.9)
	2	2	3.3 (0.8-13.2)	2	6.4 (1.6-25.9)	0	-
Active cancer	0	102	8.6 (6.9-10.8)	55	9.3 (6.8-12.5)	47	7.9 (5.7-11.0)
	1	15	16.7 (9.9-28.0)	12	25.3 (14.1-45.4)	3	7.0 (2.2-22.0)
	2	9	-	0	-	0	-

HRs adjusted for age and sex

Gran et al. Haematologica 2016;101:1046-1053

Studies on FV Leiden and cancer-related VTE

Study	Study design	Study population	Risk estimate (95% CI)
Otterson et al. 1996	Cohort	353 patients with unselected cancers	OR 3.1 (0.6-14.7)
Pihusch et al. 2002	Cohort	175 patients with gastrointestinal carcinomas	RR 4.4 (1.3-14.9)
Ravin et al. 2002	Case-control	75 patients with gynecological cancers	OR 0.3 (0.1-1.7)
Paspatis et al. 2002	Case-control	74 patients with colorectal cancer 192 colonoscopically selected controls	OR 1.5 (p>0.5, NS)
Ramacciotti et al. 2003	Cohort	211 patients with unselected cancers	OR 0.6 (0.1-5.4)
Kennedy et al. 2005	Case-control	202 patients with solid cancers	OR 1.7 (0.3-10.7)
Blom et al. 2005	Case-control	205 patients with unselected cancers	OR 2.2 (0.3-17.8)
Eroglu et al. 2007	Case-control	124 patients with unselected cancers	OR 8.1 (2.4-27.1)
Curigliano et al. 2006	Case-control	25 breast cancer patients with VTE 50 breast cancer patients without VTE	OR 6.1 (1.1–34.3)
Onur et al. 2012	Case-control	78 patients with unselected cancers 50 healthy controls	OR 0.7 (0.2-8.9)
Pabinger et al. 2015	Cohort	982 patients with unselected cancers	HR 2.0 (1.0-4.0)
Gran et al. 2016	Case-cohort	2300 subjects (609 with VTE) of which 461 are patients with cancer	HR 1.9 (1.1-3.3)

FVL and the risk of CVC-related VTE in cancer

Review: CVC (Versione aggiornata)
Comparison: 01 Factor V Leiden
Outcome: 01 Factor V Leiden

Study or sub-category	Thrombosis n/N	Control n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Sifontes, 1997	1/32	0/35		4.80	3.38 (0.13, 86.01)
Knofler, 1999	4/11	3/66		5.73	12.00 (2.22, 64.93)
Ratcliffe, 1999	1/10	2/74		4.51	4.00 (0.33, 48.66)
Wermes, 1999	1/10	10/127		13.81	1.30 (0.15, 11.32)
Fijnheer, 2002	7/33	6/244		11.84	10.68 (3.34, 34.17)
Ruud, 2002	0/18	0/23			Not estimate
Mitchell, 2003	0/22	2/38		19.08	0.32 (0.01, 7.07)
Mandala, 2004	5/25	2/50		11.21	6.00 (1.07, 33.53)
Van Rodden, 2004	6/41	4/97		21.33	3.99 (1.06, 14.97)
Abdelkefi, 2005	3/9	7/106		7.68	7.07 (1.45, 34.46)
Total (95% CI)	211	860		100.00	4.60 (2.63, 8.06)

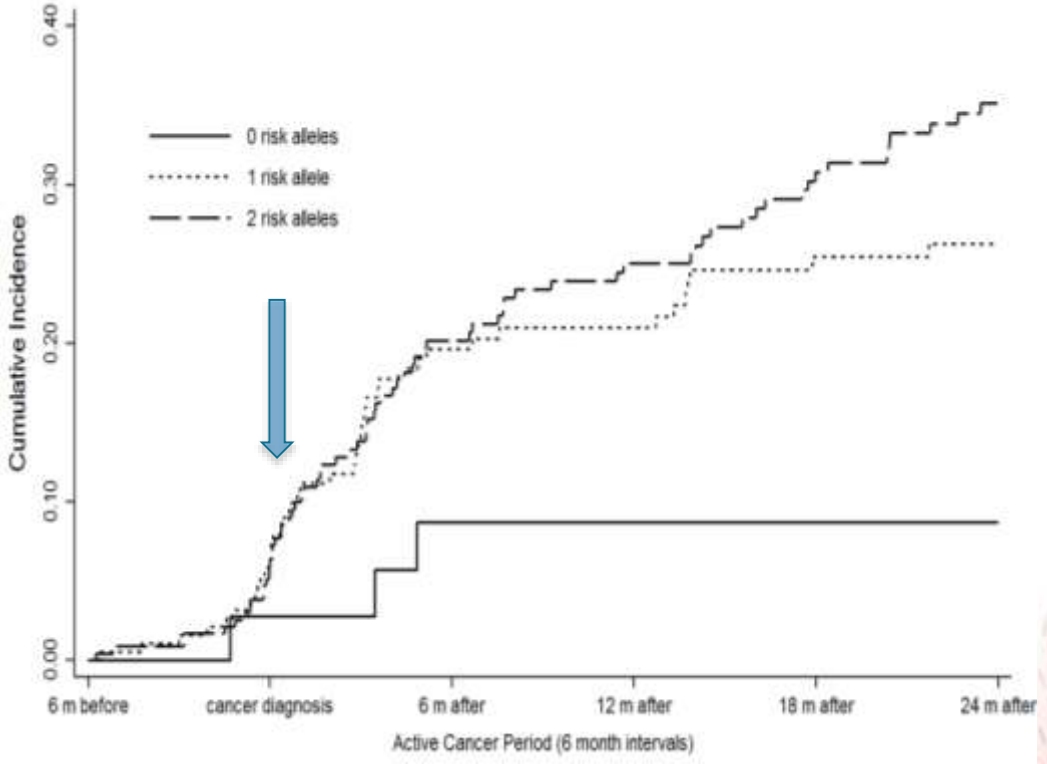
Total events: 28 (Thrombosis), 36 (Control)
Test for heterogeneity: $\chi^2 = 7.87$, df = 8 ($P = 0.45$), $I^2 = 0\%$
Test for overall effect: $Z = 5.34$ ($P < 0.00001$)

0.001 0.01 0.1 1 10 100 1000

Dentali et al, J Thromb Haemost, 2008

FV rs4524 and cancer-related VTE – The Tromsø Study

- Case-cohort study
- 609 VTE patients and a sub-cohort of 1691 individuals
- Those with FV rs4524 had a 4-fold higher risk of cancer-related VTE
- The risk was particularly high during the first 6 months after cancer diagnosis



Gran et al. Haematologica 2016;101:1046-1053

Risk of VTE according to F5 rs4524 and cancer status

Cancer status	Risk alleles	n	VTE HR (95% CI)	n	DVT HR (95% CI)	n	PE HR (95% CI)
No cancer	0	17	1.0	7	1.0	10	1.0
	1	160	1.9 (1.2-3.1)	93	2.7 (1.2-5.8)	67	1.4 (0.7-2.6)
	2	262	2.3 (1.4-3.8)	47	3.1 (1.5-6.6)	115	1.7 (0.9-3.3)
Active cancer	0	3	4.8 (1.4-16.5)	2	8.5 (1.8-41.0)	1	2.5 (0.3-19.2)
	1	44	15.9 (9.1-27.9)	26	23.9 (10.4-55.3)	18	10.4 (4.8-22.6)
	2	70	21.1 (12.4-35.8)	39	29.7 (13.3-66.6)	31	15.1 (7.4-30.9)

HRs adjusted for age and sex

Gran et al. Haematologica 2016;101:1046-1053

Studies on F2 G20210A and cancer-related VTE

Study	Study design	Study population	Risk estimate (95% CI)
Pihusch et al. 2002	Cohort	175 patients with gastrointestinal carcinomas	RR 2.4 (0.6-9.9)
Paspatis et al. 2002	Case-control	74 patients with colorectal cancer 192 colonoscopically selected controls	OR 1.51 (p>0.5, NS)
Ramacciotti et al. 2003	Cohort	211 patients with unselected cancers	OR 1.2 (0.1-13.1)
Kennedy et al. 2005	Case-control	202 patients with solid cancers	OR 6.7 (0.9-∞)
Blom et al. 2005	Case-control	205 patients with unselected cancers	OR 4.1 (0.3-17.8)
Curigliano et al. 2006	Case-control	25 breast cancer patients with VTE 50 breast cancer patients without VTE	OR 6.1 (1.1–34.3)
Mandala et al. 2009	Cohort	381 patients with breast or gastrointestinal cancers	OR 1.46 (0.18-8.38)
Onur et al. 2012	Case-control	78 patients with unselected cancers 50 healthy controls	OR 1.7 (0.5-32.5)

F2 G20210A and the risk of CVC-related VTE in cancer

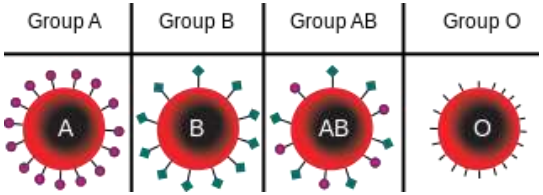
Review: CVC (Versione aggiornata)
Comparison: 02 G20210A prothrombin mutation
Outcome: 01 G201210A prothrombin mutation

Study or sub-category	Thrombosis n/N	Control n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Knofler, 1999	2/11	1/66		8.53	14.00 (1.19, 175.90)
Wermes, 1999	1/10	3/127		14.39	4.59 (0.43, 48.74)
Ruud, 2002	0/18	0/23			Not estimate
Mitchell, 2003	0/22	1/33		43.22	0.48 (0.02, 12.36)
Mandala, 2004	1/25	0/50		11.61	6.18 (0.24, 157.38)
Van Rodden, 2004	3/41	0/97		10.04	17.73 (0.89, 351.32)
Abdelkefi, 2005	0/13	1/106		12.22	2.60 (0.10, 67.21)
Total (95% CI)	140	502		100.00	4.92 (1.69, 14.26)

Total events: 7 (thrombosis), 6 (control)
Test for heterogeneity: $\chi^2 = 3.56$, df = 5 ($P = 0.61$), $I^2 = 0\%$
Test for overall effect: $Z = 2.93$ ($P = 0.003$)

0.001 0.01 0.1 1 10 100 1000

Dentali et al, J Thromb Haemost, 2008



Non-O blood type (rs8176719) and cancer-related VTE

Study	Study population	Risk estimate (95% CI)
Li et al. 2015	670 patients with pancreatic cancer	OR 1.55 (1.11-2.17) Non-O vs. O blood group
Mizrahi et al. 2015	523 children with acute lymphoblastic leukemia	OR 2.32 (1.28-4-34) Non-O vs. O blood group
Striff et al. 2004	130 patients with malignant gliomas	HR 2.7 (1.0-7.0) Non-O vs. O blood group
Moreno et al. 2009	219 pts with myeloproliferative disorders	27.1% vs. 21.9% (p=0.33) O vs. non-O blood group
Gran et al. 2018	1767 subjects from the general population and 634 VTE cases	HR 1.32 (0.95-1.83)

Other established prothrombotic genotypes and cancer-related VTE

Study	SNPs studied	Study population	Results
Eroglu et al. 2010	3 SNPs in the FVII gene	60 cancer patients with VTE and 130 cancer patients without VTE	No association with VTE.
Tiedje et al. 2011	fibrinogen -455G>A and FXIII-A Val34Leu	1079 cancer patients	No association with VTE
Onur et al. 2012	FVL, FV H1299R, FII G20210A, MTHFR C677T, MTHFR A1298C, PAI-1 4G/5G, β-fibrinogen -455 G → A, FXIII Val34Leu and GpIIIa HPA-1a	78 patients with unselected cancers 50 healthy controls	No significant association between any SNP and VTE
Bazzarelli et al. 2016	TFPI -33T→C	127 patients with colorectal cancer	VTE in 18% with TT/TC genotype and in 7% with CC genotype. **CC was also associated with improved disease-free survival.**
Ferroni et al. 2016	8 VEGF gene promoter SNPs	297 cancer patients	1154G/A (A allele) is associated with a reduced risk of VTE **and a reduced risk of early cancer progression**

Conclusions

- Patient-related factors, including biomarkers (e.g. prothrombotic genotypes), are import for cancer-related VTE
- Many prothrombotic genotypes increase the risk of cancer-related VTE
- Prothrombotic genotypes may have **differential impact on the VTE risk** in subjects without and with cancer (synergistic effects)
- **Are prothrombotic genotypes attractive biomarkers** to include in risk prediction models?

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Thank you for your attention