### Venous thromboembolism & diabetes

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# My talk today

- Pathophysiology
- Diabetes as a risk factor for VTE
- Metabolic syndrome & VTE

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# Diabetes and hypercoagulability

- Increased PAI 1 levels (Juhan-Vague et al., 1988)
- Protein C deficiency (Ceriello et al., 1990)
- Increased fibrinogen levels (Ceriello et al., 1997)
- Increased circulating soluble tissue factor (Sommeijer et al., 2007)
- Elevated prothrombin levels (Sauls et al. 2007)

### Diabetes and thrombin generation

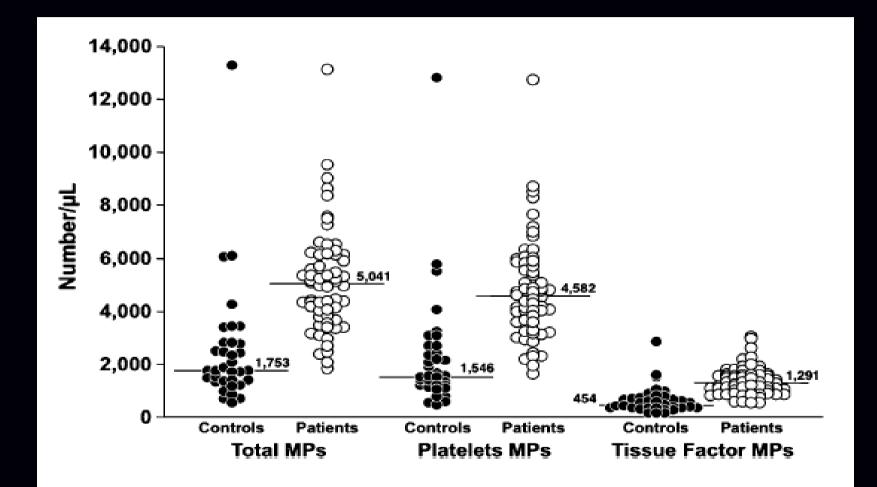
Table 2 Parameters	of thrombin generation measured in the presence
of tissue factor and p	hospholipids as coagulation triggers

Parameters	Patient $(n = 60)$ Median (range)	Controls $(n = 52)$ Median (range)	P value
Values measure	d in the absence of th	rombomodulin	
Lag-time	5.9 (4.5-11.5)	7.8 (4.7-18.4)	< 0.001
ETP	1,835 (1,213-2,656)	1,844 (1,317-2,592)	0.96
Peak	303 (207-434)	264 (97-432)	< 0.001
Time-to-peak	8.6 (6.7-15.0)	11.1 (7.8-22.3)	< 0.001
Values measure	d in the presence of th	rombomodulin	
Lag-time	7.8 (5.6-13.6)	10.4 (6.3-25.8)	< 0.001
ETP	1,497 (1,061-2,418)	1,301 (535-2,381)	0.003
Peak	297 (216-427)	256 (79-433)	0.001
Time-to-peak	10.2 (7.9-16.1)	12.9 (8.5-28.3)	< 0.001

ETP endogenous thrombin potential

Tripodi et al., J Thromb Thrombolysis 2011

### **Diabetes and circulating microparticles**



Tripodi et al., J Thromb Thrombolysis 2011

### Diabetes and hypercoagulability: tentative conclusions

- There is some evidence suggesting an activation of "blood coagulation" in patients with diabetes
- Most of the data are not "adjusted" for plausible covariates
- The evidence from prospective cohort study is limited and absent from intervention studies

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### Cardiovascular risk factors & VTE

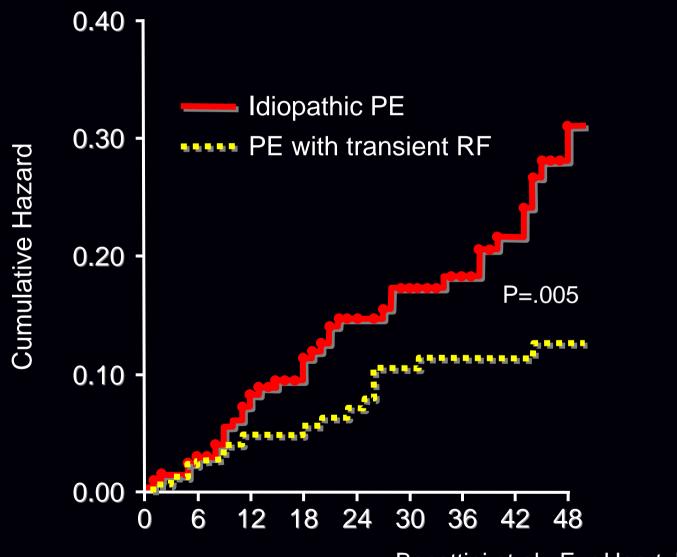
**Risk Factor** 

Hazard Ratio (95%CI)

Smoking Hypertension Diabetes Obesity Hypercholesterolemia Hypertrigliceridemia 1.03 (0.71-1.49) 1.20 (0.90-1.60) 1.70 (1.20-2.40) 2.27 (1.57-3.28) 1.03 (0.71-1.48) 1.34 (0.80-2.25)

Tsai et al., Arch Intern Med 2002

### Cardiovascular events & long-term course of PE



Becattini et al., Eur Heart J 2005

## Diabetes & VTE: as an independent risk factor

Rochester Epidemiology Project (Olmsted County)

### Cases:

Objective diagnosis of incident VTE over the period 1976-2000 (n=1922)

### Controls:

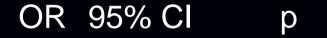
One or two residents per case, matched for age, gender and length of medical history (n=2115).

### Diabetes & VTE: univariable analysis

	OR	95% CI	р
clinically-diagnosed diabetes	1.32	1.07-1.63	0.009
diabetes with microvascular complications	1.39	0.95-2.03	0.09
diabetes with ketoacidosis	3.19	0.81-12.6	0.10
diabetes without complications	1.26	0.99-1.60	0.06

Heit et al., Arterioscler Thromb Vasc Biol. 2009

### Diabetes & VTE: multivariable analysis



defined by:clinical diagnosis0.92 0.68-1.250.59by strict blood glucose criteria0.97 0.71-1.350.87

Patients cared in hospital or nursing home in the previous three months (60% of cases compared to 15% of controls)

Heit et al., Arterioscler Thromb Vasc Biol. 2009

### Diabetes & VTE

# 2488 consecutive patients with validated VTE from the Worcester VTE Study

### 476 (19.1%) had a clinical history of diabetes

	Diabetes	No Diabetes	
	(n = 476)	(n = 2012)	P Value
Age, years (mean $\pm$ SD)	68.2 ± 14.4)	62.8 ± 18.8	<.001
Age >65 years, n (%)	309 (64.9)	1023 (50.8)	<.001
Body mass index, kg/m <sup>2</sup> (mean $\pm$ SD)	$31.0 \pm 9.2$	$28.1 \pm 7.1$	<.001
Male, n (%)	217 (45.6)	887 (44.1)	.58
Female, n (%)	259 (54.4)	1120 (55.7)	.58
Ethnicity, n (%)		and the second second second	111-1-124
Caucasian	425 (89.3)	1806 (89.8)	.76
African-American	23 (4.8)	58 (2.9)	.04
Asian	1 (0.2)	10 (0.5)	.35
Hispanic	13 (2.7)	30 (1.5)	.08
Other	4 (0.8)	17 (0.8)	.99
Unknown	10 (2.1)	91 (4.5)	.01
Developed venous thromboembolism during hospitalization for another condition, n (%)	182 (38.2)	518 (25.8)	<.001
Length of stay, days (mean $\pm$ SD)	$13.8 \pm 22.0$	9.7 ± 14.1	.001

#### Piazza et al., Am J Med 2012

### Diabetes & clinical presentation of VTE

0	Diabetes	No Diabetes	Division
	(n = 476)	(n = 2012)	P Value
Any symptoms of venous thromboembolism, n (%)	365 (76.7)	1624 (80.7)	.05
Extremity swelling, n (%)	217 (45.6)	946 (47.0)	.57
Extremity pain, n (%)	114 (24.0)	642 (31.9)	.001
Dyspnea, n (%)	106 (22.3)	457 (22.7)	,83
Tachycardia (heart rate >100 beats per minute), n (%)	57 (12.0)	199 (9.9)	.17
Cough, n (%)	38 (8.0)	153 (7.6)	.78
Chest pain, n (%)	37 (7.8)	213 (10.6)	.06
Hypotension (systolic blood pressure <100 mm Hg), n (%)	33 (6.9)	120 (6.0)	.41
Fever, n (%)	31 (6.5)	125 (6.2)	.81
Hypoxemia (oxygen saturation <90%), n (%)	12 (2.5)	43 (2.1)	.90
Loss of consciousness, n (%)	12 (2.5)	24 (1.2)	.04
Any deep vein thrombosis, n (%)	422 (88.7)	1710 (85.0)	.03
Unprovoked (idiopathic) venous thromboembolism, n (%)	79 (16.6)	547 (27.2)	<.001
Proximal lower-extremity with calf deep vein thrombosis, n (%)	66 (13.9)	243 (12.1)	,29
Proximal lower-extremity without calf deep vein thrombosis, n (%)	202 (42.4)	848 (42.2)	.91
Pulmonary embolism, n (%)	131 (27.5)	573 (28.5)	.69
Pulmonary embolism and deep vein thrombosis, n (%)	79 (16.6)	271 (13.5)	.08
Upper-extremity deep vein thrombosis, n (%)	75 (15.8)	219 (10.9)	.004
Isolated calf deep vein thrombosis, n (%)	33 (6.9)	160 (8.0)	.45

Piazza et al., Am J Med 2012

### Diabetes & long-term clinical course of VTE

Table 6         Outcomes of Patients with Venous           Thromboembolism According to History of Diabetes					
	Diabetes (n = 476)	No Diabetes $(n = 2012)$	<i>P</i> Value		
No complications, n (%) Recurrent pulmonary embolism,* n (%)	309 (64.9) 8 (1.7)	1457 (72.4) 30 (1.5)	.001 .76		
Recurrent deep vein thrombosis, * n (%)	71 (14.9)	216 (10.7)	.01		
Long-term major bleeding, * n (%)	78 (16.4)	235 (11.7)	.01		
In-hospital major bleeding, n (%)	27 (5.7)	76 (3.8)	.07		
Heparin-induced thrombocytopenia,* n (%)	6 (1.3)	19 (0.9)	.70		
In-hospital death, n (%) Death within 30 days of venous thromboembolism diagnosis, n (%)	30 (6.3) 45 (9.9)	83 (4.1) 146 (7.5)	.05 .10		

\*Long-term outcomes data encompassed a median follow-up period of 992 days.

Piazza et al., Am J Med 2012

### Diabetes & VTE

Diabetes was associated with a significant increase in the risk of recurrent DVT (14.9% vs. 10.7%; p=.01)

Diabetes was associated with a significant increase in the risk of major bleeding (16.4% vs. 11.7%; p=.01)

Aspirin therapy at discharge (aOR 1.59; 95% CI, 1.1-2.3) and chronic kidney disease (aOR 2.19; 95% CI, 1.44-3.35) were independent predictors of major bleeding

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# Metabolic syndromes & VTE

	Idiopathic VTE	Secondary VTE	Controls
Subjects	103	102	107
Subjects			
Age	65.3	62.2	63.7
Males*	58.2%	50.0%	39.2%
Mean BMI	28.1%	26.7%	26.7%
Smoking	14.5%	11.7%	19.6%

\*p = 0.02

Ageno et al., Circulation 2008

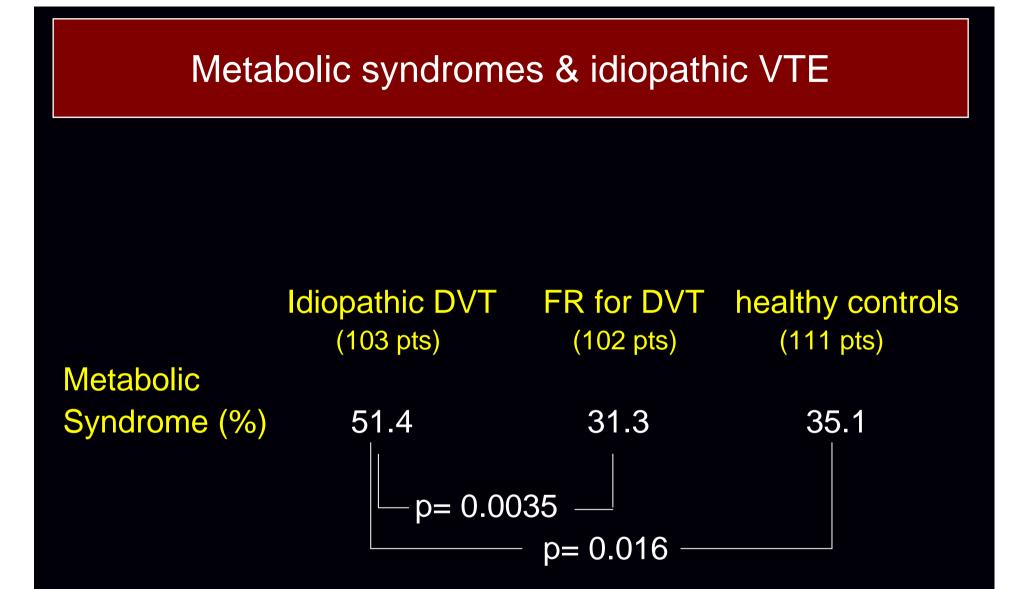
### Metabolic syndromes & idiopathic VTE

### Metabolic syndrome (%)

Idiopathic	51.4%
Secondary*	31.3%
Controls°	34.5%

\* OR 2.31 (1.26-4.27) ° OR 2.00 (1.10-3.63)

Ageno et al., Circulation 2008



Ageno et al., Circulation 2008

# Cardiovascular risk factors & VTE: diabetes mellitus

Study or sub-category	Cases n/N	Controls n/N	OR 95% CI	Weight %	OR (random) 95% Cl	
01 Case-control Study						
Poulter 1995	26/1143	51/2998	_ <b>_</b>	17.57	1.35 [0.83, 2.17]	
Hoibraaten 1998	16/176	15/352		8.59	2.25 [1.08, 4.66]	
McColl 2000	0/62	0/98			Not estimable	
Lidegaard 2002	2/987	15/4054		2.27	0.55 [0.12, 2.39]	
Prandoni 2003	28/299	18/150		11.18	0.76 [0.40, 1.42]	
Deguchi 2005	1/49	0/49		0.49	3.06 [0.12, 77.02]	
Subtotal (95% CI)	2716	7701	-	40.09	1.22 [0.75, 1.96]	
Total events: 73 (Cases), 99 (C	ontrols)		-			
Test for heterogeneity: Chi <sup>e</sup> = 6.	52, df = 4 (P = 0.16), l≏ = 3	38.6%				
Test for overall effect Z = 0.80	(P = 0.42)					
02 Cohort Study						
Tsai 2002	59/2823	243/18645	-	35.16	1.62 [1.21, 2.15]	
Cushman 2004	14/243	720/16365		14.20	1.33 [0.77, 2.29]	
Frederiksen 2004	10/208	230/7656		10.55	1.63 [0.85, 3.12]	
Subtotal (95% CI)	3274	42666		59.91	1.56 [1.23, 1.98]	
Total events: 83 (Cases), 1193		42000	· · · · · ·	55.51	1.50 [1.25, 1.50]	
Test for heterogeneity: Chi <sup>2</sup> = 0.		)%				
Test for overall effect: Z = 3.68						
	(1 = 0.0002)					
Total (95% CI)	5990	50367		100.00	1.41 [1.12, 1.77]	
Total events: 156 (Cases), 1292	(Controls)				. , .	
Test for heterogeneity: Chi <sup>e</sup> = 8.		15.2%				
Test for overall effect: Z = 2.98						
		(	0.1 0.2 0.5 1 2 6	5 10		
			Controls Cases			

Ageno et al. Circulation 2008

### Cardiovascular risk factors & VTE: obesity

or sub-category	n/N	Controls n/N	OR 95% CI	Weight %	OR (random) 95% Cl	
01 Case-control Study						
Nightingale 2000	53/394	104/1364	_ <b></b>	12.73	1.88 [1.32, 2.68]	
Lidegaard 2002	173/987	204/4054		⊢ 13.99	4.01 [3.23, 4.98]	
Vaya 2002b	24/109	13/121		- 8.57	2.35 [1.13, 4.88]	
Abdollahi 2003	102/454	62/454	_ <b></b>	12.78	1.83 [1.30, 2.59]	
Gonzalez 2003	68/126	33/125		10.75	3.27 [1.92, 5.55]	
Paganin 2003	14/46	4/92	_	5.10	9.63 [2.95, 31.40]	
Prandoni 2003	23/299	16/150		9.20	0.70 [0.36, 1.36]	
Sydney 2004	99/196	205/746		13.03	2.69 [1.95, 3.72]	
Subtotal (95% CI)	2611	7106		86.15	2.43 [1.67, 3.53]	
Total events: 556 (Cases), 641 ( Test for heterogeneity: $Chi^2 = 42$ Test for overall effect: $Z = 4.67$ (	.54, df = 7 (P < 0.00001),	I² = 83.5%				
02 Cohort study						
Tsai 2002	115/5514	189/16166		13.85	1.80 [1.43, 2.27]	
Subtotal (95% CI)	5514	16166		13.85	1.80 [1.43, 2.27]	
Total events: 115 (Cases), 189 ( Test for heterogeneity: not applic Test for overall effect: Z = 4.93 (	Controls) cable	10100		13.65	1.80 [1.43, 2.27]	
Total (95% CI) Total events: 671 (Cases), 830 ( Test for heterogeneity: Chi <sup>2</sup> = 51 Test for overall effect: Z = 5.03 (	.65, df = 8 (P < 0.00001),	23272 I <sup>e</sup> = 84.5%		100.00	2.33 [1.68, 3.24]	
			0.1 0.2 0.5 1 2	5 10		
			Controls Cases	v IV		

Ageno et al. Circulation 2008

### Cardiovascular risk factors & VTE: hypertension

Study or sub-category	Cases n/N	Controls n/N	OR 95% Cl	Weight %	OR (random) 95% Cl	
01 Case-control Study						
Poulter 1995	69/1143	120/2998	PRICES HERE &	14.66	1.54 [1.14, 2.09]	
Hoibraaten 1998	37/176	70/352		10.63	1.07 [0.69, 1.68]	
Nightingale 2000	24/394	51/1364		9.45	1.67 [1.01, 2.75]	
Lidegaard 2002	30/987	58/4054		10.65	2.16 [1.38, 3.37]	
Vaya 2002b	11/109	10/121		4.16	1.25 [0.51, 3.06]	
Prandoni 2003	83/299	46/150		11.07	0.87 [0.57, 1.33]	
Deguchi 2005	3/49	0/49		• 0.46	7.45 [0.37, 148.20]	
Subtotal (95% CI)	3157	9088		61.09	1.40 [1.06, 1.84]	
Total events: 257 (Cases),	355 (Controls)		-			
Test for heterogeneity: Chi2	= 11.87, df = 6 (P = 0.06), l <sup>2</sup> = 49	.5%				
Test for overall effect: Z = 2	.38 (P = 0.02)					
02 Cohort Study						
Hanson 1999	20/65	214/786		8.43	1.19 [0.69, 2.06]	
Tsai 2002	167/9383	136/12212		17.12	1.61 [1.28, 2.02]	
Frederiksen 2004	42/208	765/7656		13.36	2.28 [1.61, 3.22]	
Subtotal (95% CI)	9656	20654		38.91	1.70 [1.25, 2.32]	
Total events: 229 (Cases),	1115 (Controls)					
Test for heterogeneity: Chi <sup>2</sup> Test for overall effect: Z = 3	= 4.64, df = 2 (P = 0.10), l <sup>2</sup> = 56. .35 (P = 0.0008)	9%				
Total (95% CI)	12813	29742		100.00	1.51 [1.23, 1.85]	
Total events: 486 (Cases),		20142		100.00	1.51 [1.15, 1.05]	
1 17	= 18.89, df = 9 (P = 0.03), l <sup>2</sup> = 52	4%				
Test for overall effect: Z = 3		. 1 /9				
			0.1 0.2 0.5 1 2 5	10		
			Controls Cases			

Ageno et al. Circulation 2008

### Renal failure & VTE

study	VTE	CKD	Participants	Hazard ratio (95% CI)	% Weigh
Overall VTE	2				
ARIC	260	1516	11414		) 22.05
CHS	59	1392	3156		) 14.74
HUNT2	181	3487	11246	1.16 (0.84, 1.61	) 22.84
PREVEND	121	1133	8540	2.32 (1.54, 3.50	) 19.52
Tromso	225	593	6797	1.73 (1.19, 2.52	) 20.84
Subtotal (I-	squared	d = 64.3	6, p = 0.024)	1.54 (1.15, 2.06	) 100.00
<ul> <li>1</li> </ul>					
Unprovoked	d VTE				
ARIC	92	1488	11246	1.09 (0.60, 1.96	) 20.59
CHS	20	1370	3116	2.42 (0.92, 6.32	) 10.88
HUNT2	104	3447	11169	1.04 (0.68, 1.60	) 27.75
PREVEND	60	1115	8479	2.41 (1.37, 4.24	) 21.52
Tromso	90	570	6662	1.52 (0.81, 2.84	) 19.26
Subtotal (I-	squared	d = 45.8°	%, p = 0.117)	1.48 (1.03, 2.13	) 100.00
••					
Provoked V	TE				
ARIC	168	1502	11322	1.11 (0.72, 1.69	) 27.63
CHS	39	1379	3135	1.75 (0.88, 3.48	) 12.31
HUNT2	77	3444	11142	1.36 (0.82, 2.24	) 21.03
PREVEND	61	1109	8480		) 15.60
Tromso	135	581	6707	1.88 (1.17, 3.00	) 23.43
Subtotal (I-	squared	$d = 16.9^{\circ}$	%, p = 0.307)	1.54 (1.19, 1.99	) 100.00
NOTE: Wei-	late are	from co.	dom offecto enclusie		
NOTE: Weig	uns are	nom ra	dom effects analysis		
				-+	
			.2 .5	1 2 5	
			Lower Risk	Higher Risk	

### Mahmoodi et al., Circulation 2012

### Venous thromboembolism & diabetes

- The role of diabetes as risk factor for VTE remains unclear (and should be probably seen within the metabolic syndrome)
- Diabetic patients with VTE have an increased risk for recurrence and major bleeding
- Prophylaxis is underused in diabetic patients who were hospitalized for medical or surgical conditions