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

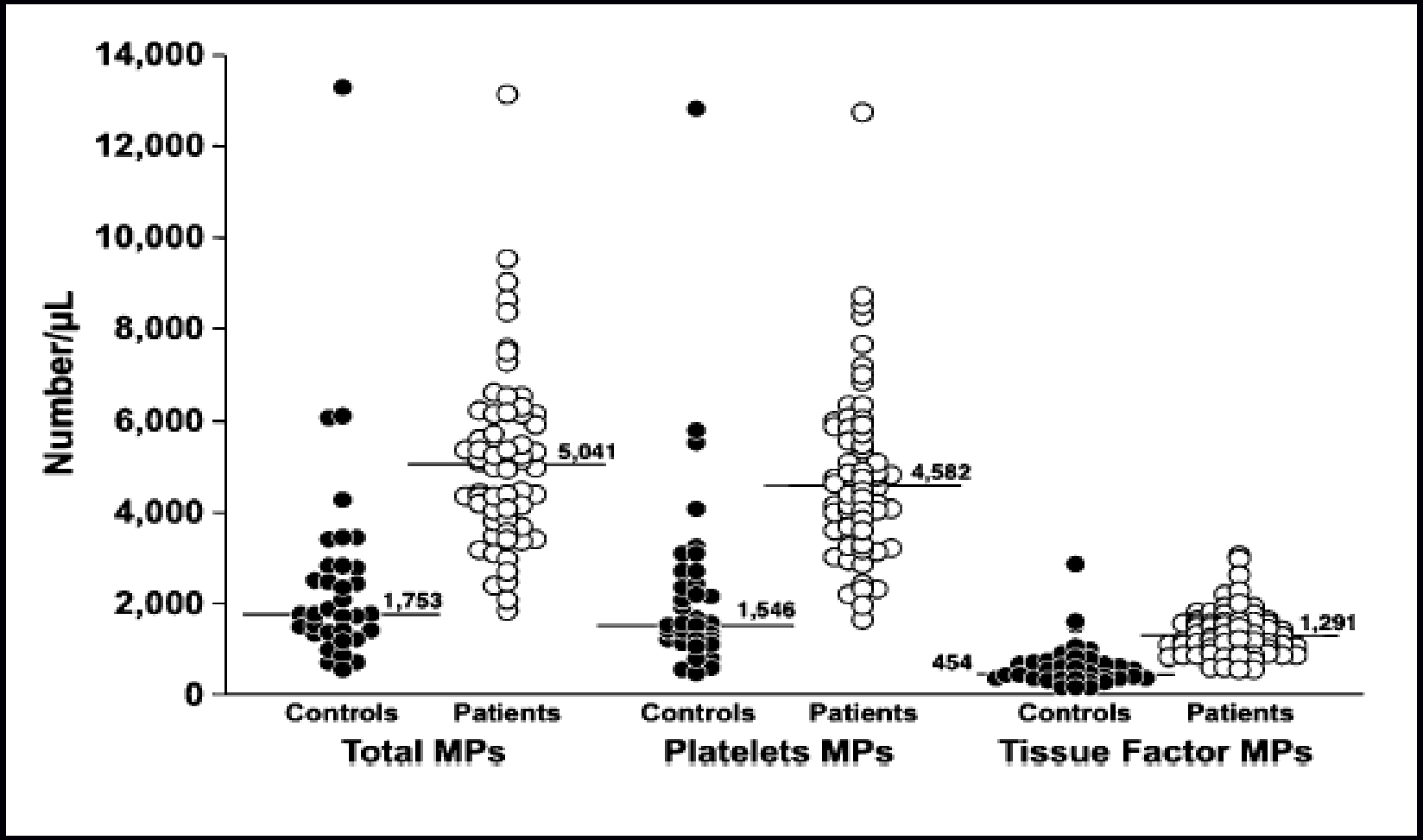
Table 2 Parameters of thrombin generation measured in the presence of tissue factor and phospholipids as coagulation triggers

Parameters	Patient ($n = 60$) Median (range)	Controls ($n = 52$) Median (range)	P value
Values measured in the absence of thrombomodulin			
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 measured in the presence of thrombomodulin			
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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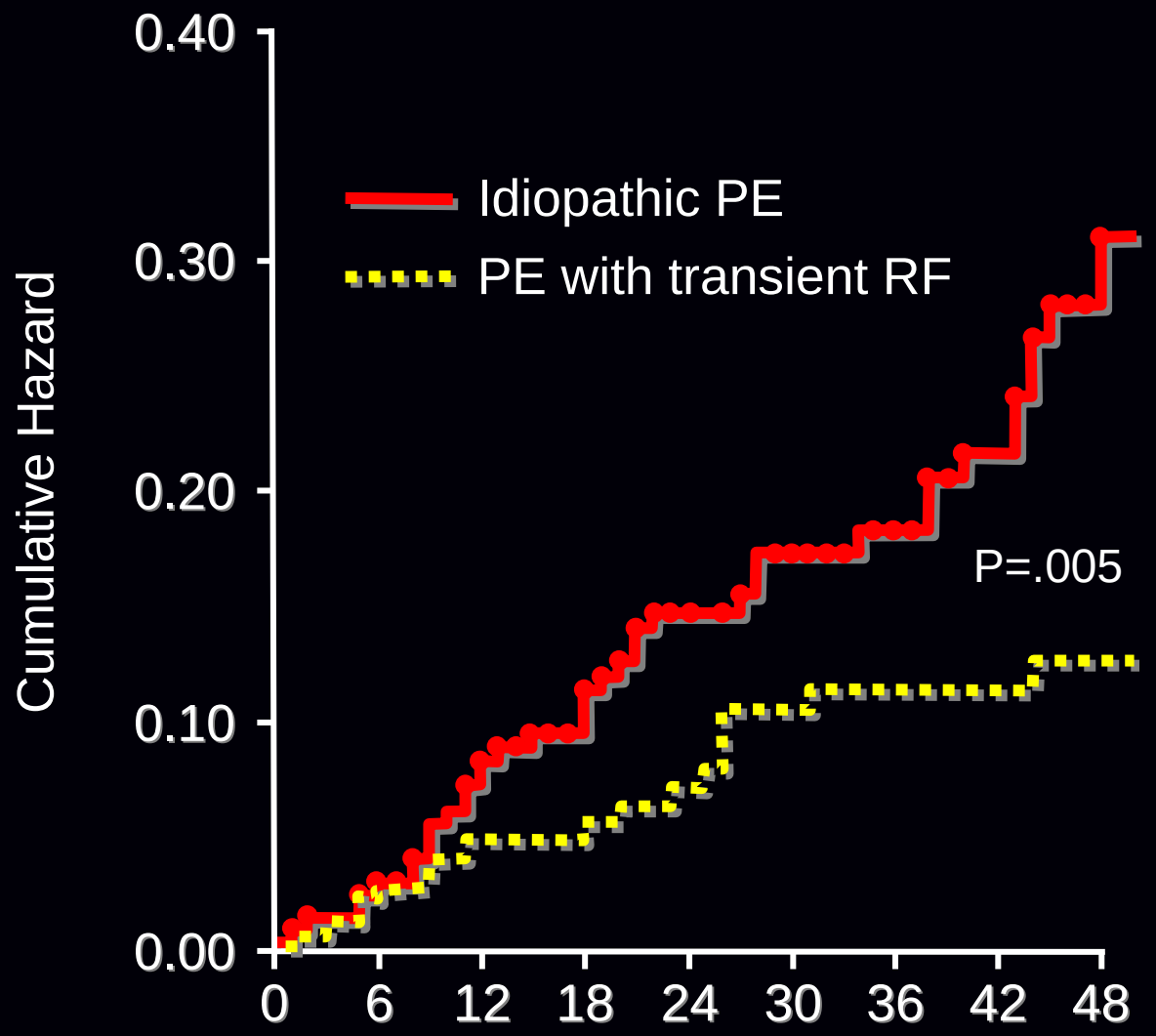
Cardiovascular risk factors & VTE

Risk Factor	Hazard Ratio (95%CI)
Smoking	1.03 (0.71-1.49)
Hypertension	1.20 (0.90-1.60)
Diabetes	1.70 (1.20-2.40)
Obesity	2.27 (1.57-3.28)
Hypercholesterolemia	1.03 (0.71-1.48)
Hypertrigliceridemia	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).

Heit et al., Arterioscler Thromb Vasc Biol. 2009

Diabetes & VTE: univariable analysis

	OR	95% CI	p
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

	OR	95% CI	p
defined by:			
clinical diagnosis	0.92	0.68-1.25	0.59
by strict blood glucose criteria	0.97	0.71-1.35	0.87

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 (n = 476)	No Diabetes (n = 2012)	*P* Value
Age, years (mean ± 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^2 (mean ± SD)	31.0 ± 9.2	28.1 ± 7.1	<.001
Male, n (%)	217 (45.6)	887 (44.1)	.58
Female, n (%)	259 (54.4)	1120 (55.7)	.58
Ethnicity, n (%)			
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 ± SD)	13.8 ± 22.0	9.7 ± 14.1	.001

Piazza et al., Am J Med 2012

Diabetes & clinical presentation of VTE

	Diabetes (n = 476)	No Diabetes (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)	*P* Value
No complications, n (%)	309 (64.9)	1457 (72.4)	.001
Recurrent pulmonary embolism,* n (%)	8 (1.7)	30 (1.5)	.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 (%)	30 (6.3)	83 (4.1)	.05
Death within 30 days of venous thromboembolism diagnosis, n (%)	45 (9.9)	146 (7.5)	.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

Piazza et al., Am J Med 2012

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Metabolic syndromes & VTE

	Idiopathic VTE	Secondary VTE	Controls
Subjects	103	102	107
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

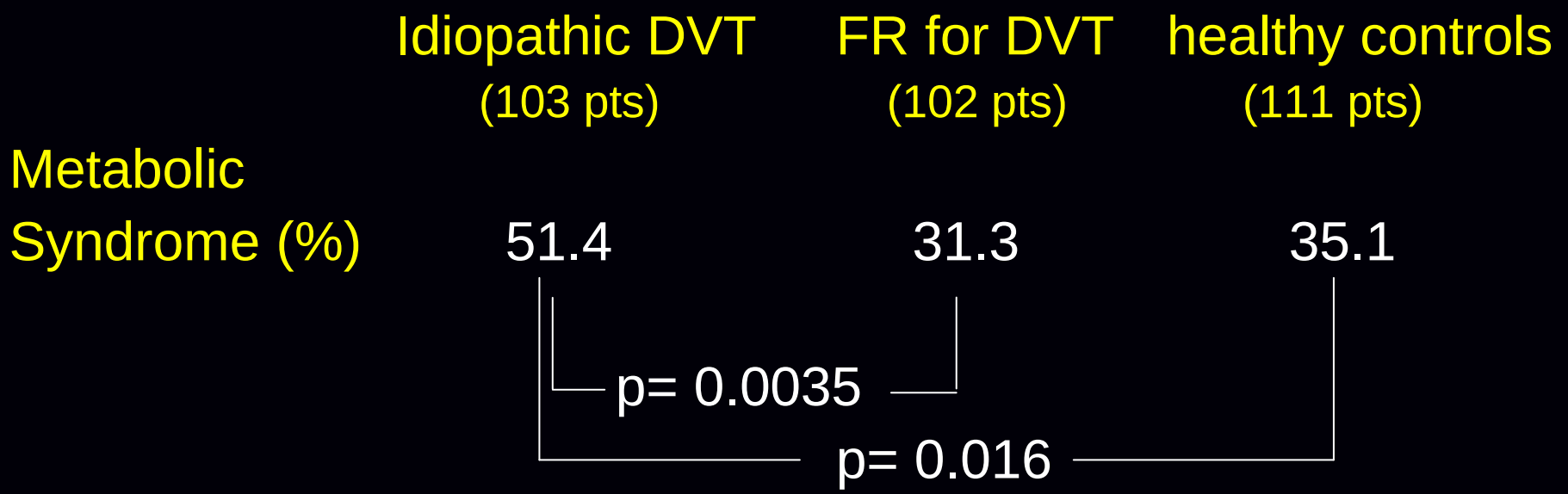
	Metabolic syndrome (%)
Idiopathic	51.4%
Secondary*	31.3%
Controls°	34.5%

* OR 2.31 (1.26-4.27)

° OR 2.00 (1.10-3.63)

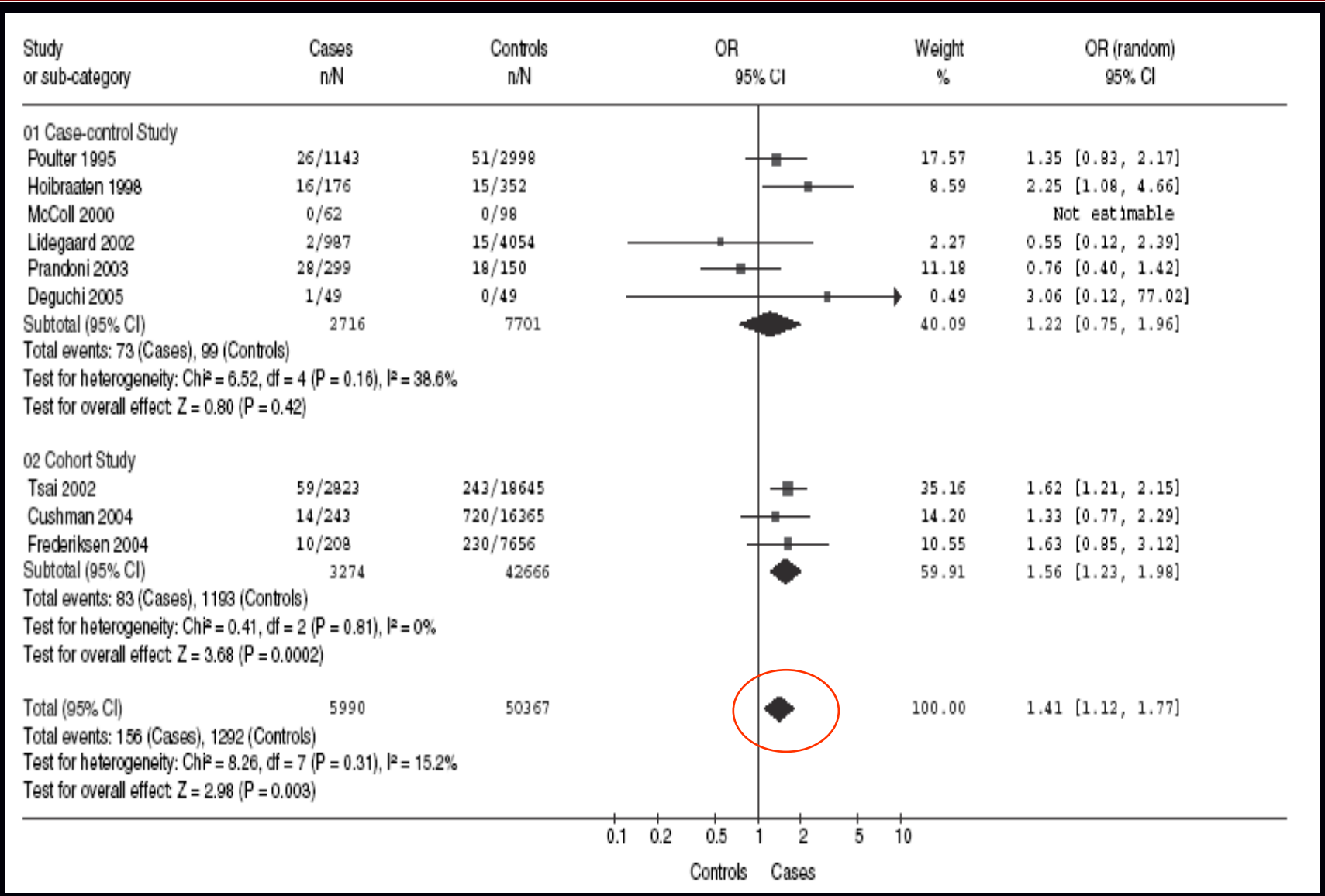
Ageno et al., Circulation 2008

Metabolic syndromes & idiopathic VTE



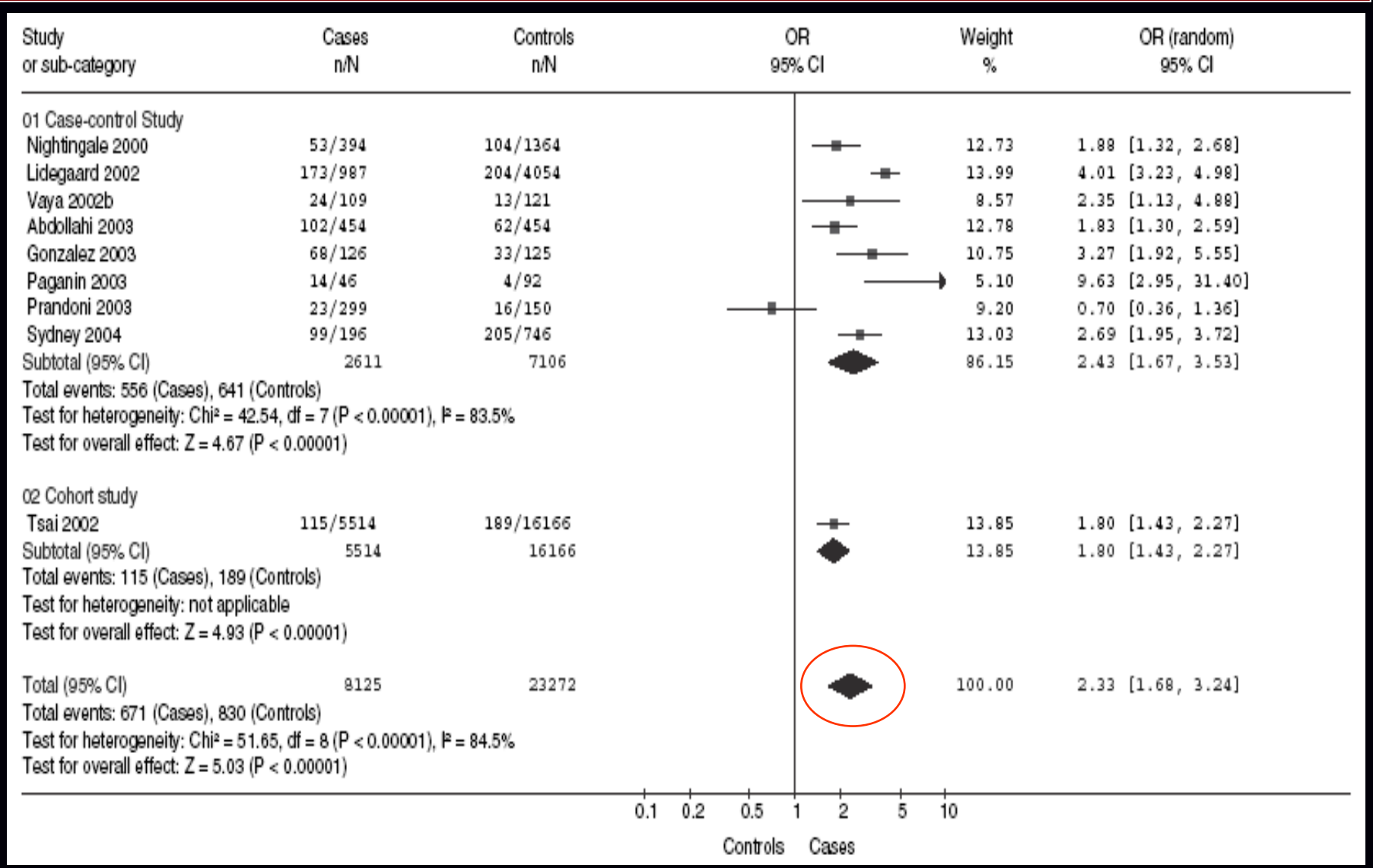
Ageno et al., Circulation 2008

Cardiovascular risk factors & VTE: diabetes mellitus



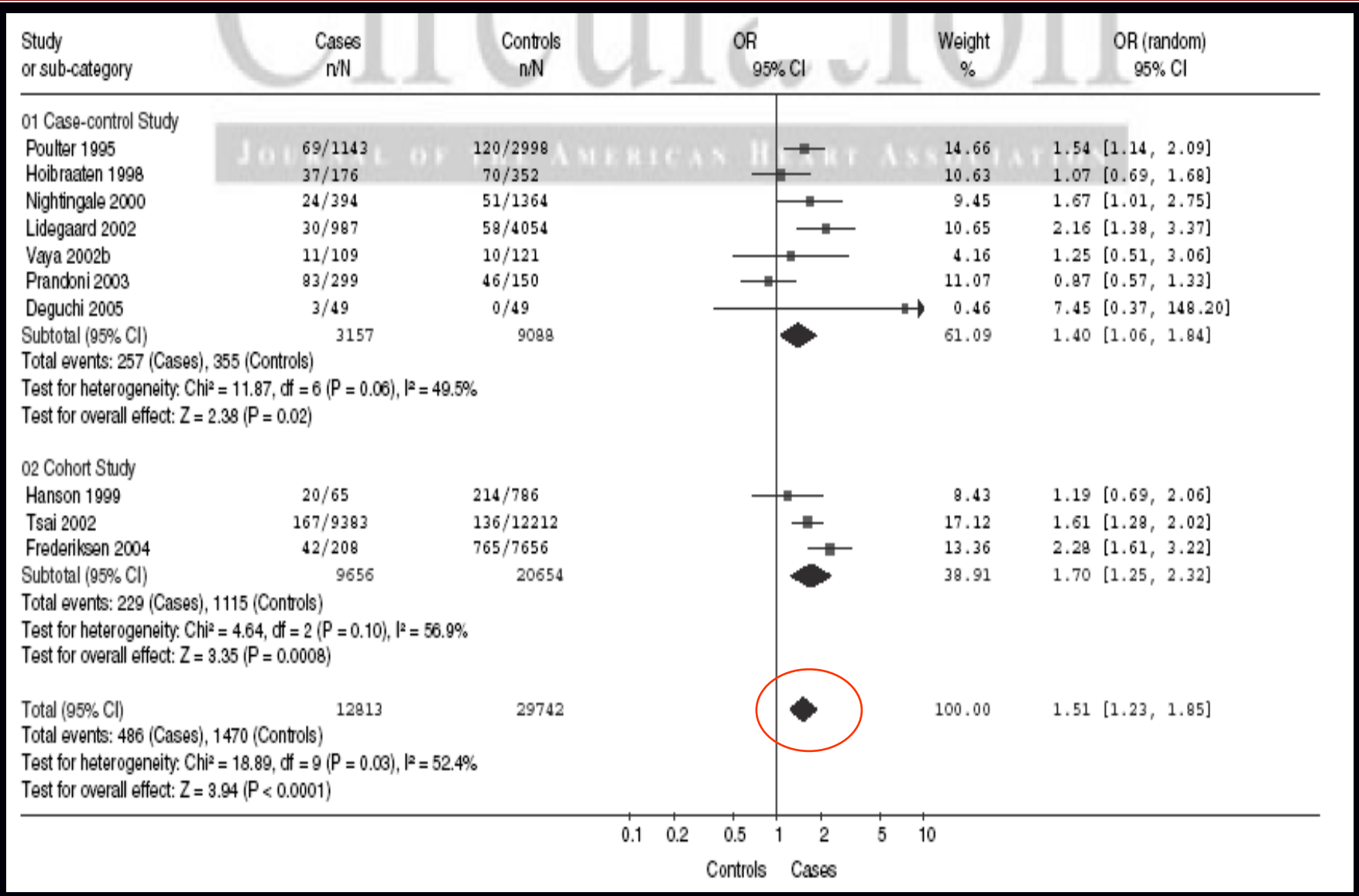
Ageno et al. Circulation 2008

Cardiovascular risk factors & VTE: obesity



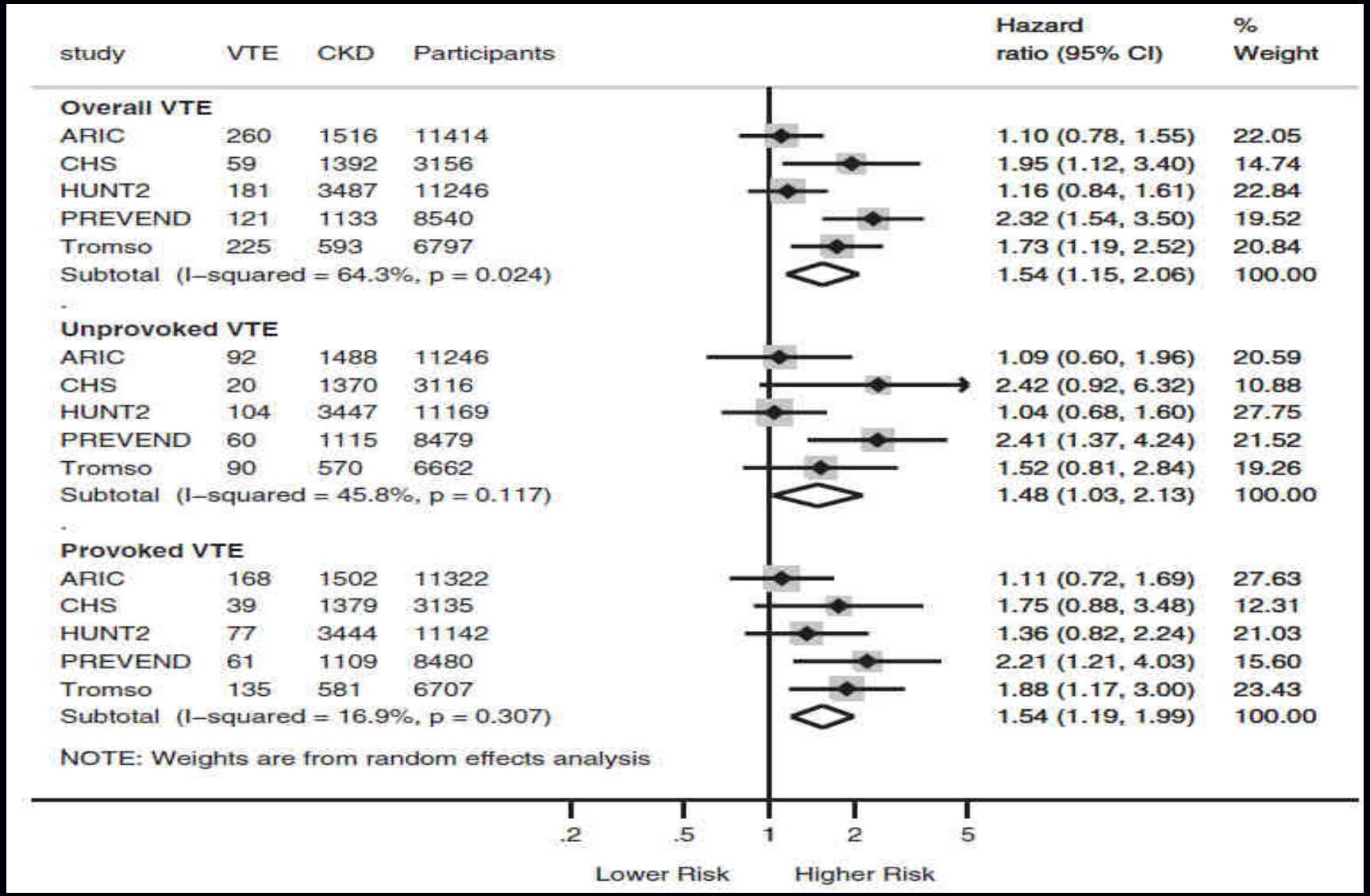
Ageno et al. Circulation 2008

Cardiovascular risk factors & VTE: hypertension



Ageno et al. Circulation 2008

Renal failure & VTE



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