

# Cancer and atherosclerosis – high risk diseases associated with venous thromboembolic disease

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## Abstract

VTE: venous thromboembolic disease, DVT: deep venous thrombosis, PE: pulmonary embolism, PFO: patent foramen ovale, CTEPH: chronic thromboembolic pulmonary hypertension

## Introduction

Venous thromboembolic disease (VTE) is primarily associated with embolus formation within veins. The thrombus can flow with the bloodstream to the pulmonary arteries causing the pulmonary embolism (PE), which represents a significant source of mortality. Therapeutic anticoagulation is the cornerstone of management in all patients with VTE. It allows decreasing the mortality due to PE and the rate of the recurrent VTE episodes. However, some patients with PE will die due to comorbidities. There is rising concern about the common incidence of VTE and other medical conditions associated with a fatal outcome like cancer or atherosclerosis.

## The risk of neoplasm after thromboembolic event

The venous thromboembolic disease may appear as a first manifestation malignancy. This phenomenon has been described for the first time by Armand Trousseau in 1865. Interest areas of research include particularly the incidence of cancer after the diagnosis of VTE and the probability of the existence of a factor that induces proliferative process in the group of patients with VTE.

In the study based on data from the Danish National Registry of Patients 15,348 patients were diagnosed with DVT and 11,305 patients with PE. For both groups of patients standardized incidence ratio (Observed Cases/Expected Cases) for all types of cancers was 1.3. The risk of cancer was significantly elevated only during the first six months of follow-up and declined rapidly thereafter to a steady level slightly above 1.0 (standardized incidence ratio) one year after the thrombotic episode. Unfortunately, forty percent of patients with diagnosed cancer within the first year from hospitalization for VTE had remote metastases at the time of the diagnosis of cancer. This study has shown the strong association between VTE and incidence of several cancers, including particularly those of the pancreas, ovary, liver and brain [1].

In another study authors analyzed the group of patients with the first episode of VTE, who had not been diagnosed with cancer up to three months after VTE and who followed for 120 months. The annual risk of a new cancer was 1.32 (95%CI, 1.09–1.60) per 100 person-years during follow-up and was not significantly higher for patients after the episode of recurrent non-fatal VTE (1.26 (95%CI, 0.72–2.06)/ 100

person-years). The incidence of new cancer in all groups of patients remained constant over time, without an increased risk of new cancer during the 3-12 months period after VTE occurrence. The risk of cancer for patients with unprovoked VTE was more than 2-fold higher as compared with those with provoked VTE. The annual risk for new cancer for these groups was 1.76 (95%CI, 1.39–2.20) per 100 person-years and 0.83 (95%CI, 0.58–1.16) per 100 person-years ( $p = 0.00084$ ), respectively. Researchers identified two independent risk factors for cancer incidence: unprovoked VTE (HR, 1.86; 95%CI, 1.21–2.87) and age (for 10-year increments HR, 1.23; 95%CI, 1.05–1.44). Risk factors such as patient sex, history of thrombophilia, recurrent VTE and the duration of anticoagulant therapy had not a considerable influence on the incidence of new cancer. The occurrence of both deep vein thrombosis and pulmonary embolism compared with isolated pulmonary embolism is not associated with significantly increased risk for new cancer (HR, 1.73; 95%CI, 0.89–3.37) [2].

In a prospective, randomized trial dedicated to the assessment of duration of anticoagulation therapy in patients after first episode of DVT, new cancer developed in 111 out of 854 patients (13%) during 8.1 years of follow-up. The standardized incidence ratio for new cancer was 3.4 (95 % CI, 2.2–4.6) during the first year after DVT episode and remained on a stable level between 1.3 to 2.2 (standardized incidence ratio) over the following five years. Older age and unprovoked DVT was also in this study independent risk factors for cancer. An interesting observation was significantly higher incidence of new cancer in patients receiving anticoagulant therapy only for six weeks in comparison to a group of patients treated for six months ( $P=0.02$ ) [3].

There are several studies conducted to investigate advantages of extensive screening for occult cancer in patients with DVT or PE [5–10]. In a systemic review of fifteen publications focused on screening for cancer in patients with VTE estimated prevalence of previously

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**Table 1.** The risk of neoplasm after thromboembolic event

Study	Population	Follow-up (months/ years)	VTE form	Cancer incidence/ SIR (95%CI)/ OR (95%CI)	HR (95%CI)
Sørensen et al. The Risk of a Diagnosis of Cancer after Primary Deep Venous Thrombosis or Pulmonary Embolism N Engl J Med 1998; 338:1169-1173	26 653 DVT - 15 348 PE - 11 305	DVT–6.1 years PE – 3.6 years	DVT	1737/1.3 (1.21-1.33)	
			PE	730/1.3 (1.22-1.41)	
Douketis et al. The long-term risk of cancer in patients with a first episode of venous thromboembolism. J Thromb Haemost 2009; 7: 546–51.	1 852	Patient-years follow-up	VTE form	New cancers per 100 person years of follow-up (Events/ Estimate (95% CI)	
		5230	DVT - 1199	64/ 1.22 (0.95–1.55)	vs. PE 1.15 (0.63–2.69); p=0.65 (univariable analysis)
		1175	PE - 302	13/ 1.11 (0.62–1.84)	
		1525	DVT and PE - 351	28/ 1.84 (1.25–2.62)	vs. PE 1.71 (0.89–3.32); p=0.11 (univariable analysis)
		4200	Unprovoked VTE - 1016	74/ 1.76 (1.39–2.20)	vs. provoked 2.09 (1.37–3.17); p=0.0006 (univariable analysis) 2.09 (1.37–3.17); p=0.0006 (univariable analysis)
		3731	Provoked VTE – 836	31/ 0.83 (0.58–1.16)	
Monreal M, et al. Screening for occult cancer in patients with acute deep vein thrombosis or pulmonary embolism. J Thromb Haemost 2004; 2: 876–81.	830	12 months	PE	OR (95%CI) 1.42 (0.53–3.62); p =N.S.	
			Proximal DVT	OR (95%CI) 1.13 (0.40–3.46); p =N.S.	
			Recurrence VTE	OR (95%CI) 0.60 (0.17–1.87); p =N.S.	
			Unprovoked VTE	OR (95%CI) 3.32 (1.39–8.09); p = <0.01	
Schulman S, Lindmarker P. et. al Incidence of cancer after prophylaxis with warfarin against recurrent venous thromboembolism. Duration of Anticoagulation Trial. N Engl J Med. 2000 Jun 29;342(26):1953-8.	854	8.1 years	DVT	111 (13% during follow –up)/ SIR 3.4 (2.2 – 4.6) during first year follow-up SIR 1.3-2.2 – during further five years follow-up	
			Unprovoked DVT	OR 1.5 (95%CI, 1.2-2.0; p<0.001)	
			Recurrence DVT	OR 1.3 (95% CI, 1.0 -1.6; p= 0.02	
Ryma Ihaddadene et. al Risk factors predictive of occult cancer detection in patients with unprovoked venous thromboembolism Blood 2016 127:2035-2037	854	1 year	DVT	24 (72.7%)	Univariate analysis HR 1.89 (0.88-4.07) p=0.104 Absolute risk = 5.1%
			PE	7 (21.2%)	Univariate analysis HR 0.60 (0.26-1.38) p=0.229 Absolute risk = 2.5%
			DVT+PE	2 (6.1%)	Univariate analysis HR 0.54 (0.13-2.24) p=0.392 Absolute risk = 1.9%
			Previously diagnosed provoked VTE	5 (15.2%)	Univariate analysis HR 3.57 (1.38-9.25) p=0.009 Absolute risk = 10.6%

HR – hazard ratio; OR – odds ratio, SIR - standardized incidence ratio; N.S. - not significant

undiagnosed cancer in patients with unprovoked VTE was 6.1% (95%CI, 5.0-7.1) at the onset of VTE and 10.0% (95%CI, 8.6-11.3) in the period from thrombotic event up to 12 months. For the provoked VTE prevalence were 1.9% (95%CI, 1.3-2.5) and 2.6% (95%CI, 1.6-3.6), respectively [5].

### The risk of stroke after thromboembolic event

Stroke is one of the most common cause of mortality but also disability of affected patients. According to results of the INTERSTROKE study five following factors: hypertension, current

**Table 2.** The risk of stroke after thromboembolic event

Study	Population	Follow-up (months/ years)	VTE form	Stroke incidence		RR (95%CI)/ ARR (95%CI)			
Cecilia Becattini et. al A prospective study on cardiovascular events after acute pulmonary embolism, European Heart Journal (2005) 26, 77–83	360	38 months	Unprovoked PE	* n(%) = 5 (0.8)		RR 3.61 (0.43 – 30.61) p=0.21			
			Provoked PE	* n(%) = 1 (0.2)					
Frederikus A. et al. Risk of arterial cardiovascular events in patients after pulmonary embolism Blood 2009 114:1484-1488.	Patients with unprovoked PE – 95 Patients with provoked PE – 259 Control group – 334	4.2 years	Unprovoked PE+ Provoked PE	* n(%) = 21 (1.3)		RR vs control group 2.35 (0.93-6.0)			
			Unprovoked PE	* n(%) = 9 (3.7)	RR vs control group 5.27 (1.9-14)				
					RR vs provoked PE 4.09 (1.5-11)				
Provoked PE	* n(%) = 6 (0.92)	RR vs control group 1.29 (0.42-4.0)							
		Henrik Toft Sørensen et. al <i>Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study, Lancet 2007; 370: 1773–79.</i>	Patients with DVT– 25 199 Patients with PE – 16 925 Control group – 163 566	20 years		First year	Subsequent 2-20 years of follow-up	First year	Subsequent 2-20 years of follow-up
								ARR (95%CI)	ARR (95%CI)
DVT	209				1367	2.19 (1.85–2.60)	1.31 (1.23–1.39)		
PE	113				608	2.93 (2.34–3.66)	1.29 (1.18–1.40)		
Unprovoked DVT	137				1118	2.01 (1.63–2.48)	1.29 (1.21–1.38)		
Provoked DVT	72				249	2.62 (1.84–3.73)	1.38 (1.10–1.73)		
Unprovoked PE	84				488	3.17 (2.41–4.17)	1.32 (1.20–1.45)		
Provoked PE	29	120	2.16 (1.33–3.50)	1.07 (0.79–1.44)					

RR – relative risk; ARR – adjusted relative risk

\* n(%) – incidence, n per 100 patient-years

**Table 3.** The risk of acute myocardial infarction after thromboembolic event

Study	Population	Follow-up (months/ years)	VTE form	Acute myocardial infarction incidence		RR (95%CI)/ ARR (95%CI)	
Cecilia Becattini et. Al A prospective study on cardiovascular events after acute pulmonary embolism, European Heart Journal (2005) 26, 77–83	360	38 months	Unprovoked PE	* n(%) = 12 (1.9)		p=0.003	
			Provoked PE	0			
Frederikus A. et al. Risk of arterial cardiovascular events in patients after pulmonary embolism Blood 2009 114:1484-1488.	Patients with unprovoked PE – 95 Patients with provoked PE – 259 Control group – 334	4.2 years	Provoked PE+ Unprovoked PE	* n(%) = 14 (0.89)		RR vs control group 2.35 (0.93-6.0)	
			Unprovoked PE	* n(%) = 6 (4.2)	RR vs control group 5.27 (1.9-14)		
					RR vs provoked PE 4.09 (1.5-11)		
			Provoked PE	* n(%) = 4 (0.4)	RR vs control group 1.29 (0.42-4.0)		
Henrik Toft Sørensen et. al Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study, Lancet 2007; 370: 1773–79.	Patients with DVT – 25 199 Patients with PE – 16 925 Control group – 163 566	20 years		First year	Subsequent 2-20 years of follow-up	First year	Subsequent 2-20 years of follow-up
						ARR (95%CI)	ARR (95%CI)
			DVT	176	1157	1.60 (1.35–1.91)	1.18 (1.11–1.26)
			PE	144	597	2.60 (2.14–3.14)	1.32 (1.21–1.43)
			Unprovoked DVT	138	961	1.74 (1.42–2.13)	1.18 (1.10–1.27)
			Provoked DVT	38	196	1.22 (0.80–1.87)	1.17 (0.89–1.53)
			Unprovoked PE	108	486	2.62 (2.09–3.29)	1.36 (1.23–1.49)
			Provoked PE	36	111	2.63 (1.67–4.14)	1.31 (0.94–1.81)

RR – relative risk; ARR – adjusted relative risk

\* n(%) – incidence, n per 100 patient-years

smoking, abdominal obesity, inadequate diet and low physical activity are responsible for above 80% of the total risk of all types of stroke [11].

In recent years growing interest on the incidence of cardiovascular events including stroke after VTE episode has been observed. The risk factors for both conditions seem to be common.

In the prospective multicenter study the incidence of cardiovascular events was analyzed in 360 patients with the history of the first PE episode. During 38 months of follow-up, 64 patients (5.5% patient-year) experienced at least one incident of cardiovascular disease. The relative risk of stroke was 3.61 (0.43 – 30.61);  $p=0.21$ . One recurrent VTE episode and one ischaemic stroke occurred while patients were anticoagulated, while all the other cardiovascular events were observed after withdrawal of anticoagulation. Stroke was noticed in 5 patients (0.8% patient-year) with unprovoked PE and 1 patient (0.2% patient-year) with provoked PE. Overall 20 patients (3.2% patient-year) with unprovoked PE and 2 patients (0.4% patient-year) with provoked PE experienced at least one cardiovascular event (AMI, stroke, and sudden unexplained death) (RR 7.2; 95% CI 1.71–30.45;  $P < 0.001$ ) [12].

The similar observation was reported as the result of cohort study analysis of the event-free survival of patients with the history of first PE episode and a group of subjects with excluded PE. Patients with unprovoked PE had higher incidence of stroke (9 events, 3.7%, RR unprovoked vs provoked 4.09 (1.5-11)) than patients with provoked PE (6 events, 0.92%) and patients without PE (6 events, 0.87%, RR unprovoked vs. controls 5.27 (1.9-14)) during 4.2 years follow-up. Furthermore, the risk of any cardiovascular event was increased in patients with unprovoked PE compared with provoked PE (RR unprovoked vs provoked 3.21 (1.8-5.8)) and patients without PE (RR unprovoked vs. controls 2.7 (1.6-4.6)) [13].

In the large Danish cohort study risk of myocardial infarction and stroke was evaluated in 25 199 patients with DVT and 16 925 patients with PE compared with 165 566 patients from control group during 20-years follow-up. The relative risk of stroke after DVT was 2.19 (95% CI 1.85–2.60) during the first year of follow-up and was slightly higher for PE 2.93 (95% CI 2.34–3.66). The relative risk of myocardial infarction or stroke during 1 to 5 years of follow-up was 1.33 (95% CI 1.24–1.43) and has declined steadily to 1.14 (95% CI 0.99–1.31) in the period of 16–20 years after thrombosis event, whereas the relative risk after PE was similar during these two periods. The relative risk decreased slowly during long term follow-up after unprovoked DVT, while for unprovoked PE the relative risk remained more stable. The excess risk of cardiovascular events for DVT as well as PE was most noticeable during the first year of follow-up and levelled off over a 20-year period. On contrary to results of cited studies the relative risk was similar for patients with provoked and unprovoked VTE [14].

PE has a substantial association with higher incidence of paradoxical embolism in patients with patent foramen ovale (PFO). In the study of Konstantinides et al. patients with PE and concurrent PFO had significantly higher risk of ischaemic stroke (13% vs. 2.2%;  $p=0.02$ ) [15]. In the research conducted in our centre, an acute ischaemic stroke confirmed by magnetic resonance imaging was found in 4 patients out of 55 patients with PE (7.3%). All strokes were observed in patients with PFO (4 of 19 patients), whereas no cerebral incident was noticed in subjects with excluded PFO (21% vs 0%,  $p=0.02$ ). Moreover, all stroke episodes were detected in patients with PFO and RVD (right ventricular dysfunction), while none of patients with PFO and preserved RV function (50% vs 0%,  $p=0.038$ ) [16].

## The risk of acute myocardial infarction after thromboembolic event

Ischemic heart disease remains leading cause of death worldwide. According to a nationwide case-control INTERHEART study nine easily measured factors are responsible for above 90% of the total risk of myocardial infarction. Besides above-mentioned risk factors for stroke (hypertension, current smoking, abdominal obesity, inadequate diet and low physical activity), they include abnormal lipids, diabetes, obesity, alcohol and psychosocial factors [17].

The relative risk of myocardial infarction in DVT patients during the first year of follow-up after a thrombotic event was 1.60 (95%CI, 1.35–1.91) and also in this study was higher for patients after PE 2.60 (95%CI, 2.14–3.14). The relative risk of arterial cardiovascular events was steadily raised at 20–40% during subsequent 20 years of follow-up (14) Myocardial infarction (MI) occurred in 12 of 360 patients (1.0% patient-year) after first PE episode during 38-months follow-up [12]. MI occurred significantly more often in patients with unprovoked PE (12 patients, 1.9% patient-year) than patients with provoked PE (0 patients),  $p=0.003$ . The age above 60 years, unprovoked PE and diagnose of new cancer were associated with raised risk of cardiovascular events in univariate analysis, whereas gender, arterial hypertension, diabetes, smoking, hyperlipidemia, the presence of DVT and shorter anticoagulation (3 months) were not associated with higher risk of cardiovascular events. Unprovoked PE remains independent predictor of cardiovascular events after adjusting for age; HR (95%CI) 2.54 (1.09–5.89);  $p = 0.03$ . The authors underlined that their observation is similar to numerous published reports concerning frequent incidence of arteriosclerotic lesions in patients with unprovoked DVT [18]. A meta-analysis by W. Ageno et al. of the results of 21 studies on the incidence of main cardiovascular risk factors in patients with VTE revealed that obesity, arterial hypertension and diabetes were significant risk factors for VTE incidence compared with control group. An explanation of this phenomenon can be an influence of above factors on inflammation and prothrombotic process activation as well as abnormal endothelium function. The coexistence of those results seems to have an additive effect [19].

Recently published studies indicate the association of the chronic thromboembolic pulmonary hypertension (CTEPH), the rare complication of PE, with a higher incidence of significant coronary artery disease. The elderly patients ( $> 65$  years) with CTEPH were found to have a higher risk of chronic coronary artery disease than elderly patients after an episode of PE but without CTEPH (OR = 5.9, 95% CI: 1.64–21.46,  $p = 0.007$ ) [20].

## Discussion

The incidence of cardiovascular disease and cancer is higher in a population of patients after VTE episode. Furthermore, both of them are the most common cause of death in that group responsible for approximately 42.4% i 21.2%, respectively [12,21].

Literature review leads to the conclusion VTE is rather a complication than a risk factor for cancer. The proliferative process induces prothrombotic mechanisms, which may precede cancer up to several years before it is clinically overt. An interesting hypothesis has been proposed concerning an existence of common physiological coagulation factor, which might induce carcinogenesis or antineoplastic effect of warfarin [3,4]. Independent risk factors for cancer were older age and incidence of unprovoked VTE. However, extensive screening including CT tests is not recommended in patients with VTE episode.

The most optimal strategy includes: taking careful medical history, physical examination, basic laboratory tests and chest X-ray. [5,7]

Growing number of evidence suggest VTE and arteriosclerosis have common risk factors but also shared pathophysiology [22]. The confirmation of above observation can result in additional primary and secondary intervention to prevent both diseases at the same time.

In the group of healthy patients recruited to JUPITER study receiving rosuvastatin 20 mg daily the risk of VTE incidence has nearly halved compared to patients receiving placebo. The protective effect was noticed on prevention of both provoked and unprovoked VTE. The benefit was more marked in a prevention of DVT than PE [23]. Further evidence provided systemic review and meta-analysis by Kunutsor et al. who found VTE incidence significantly lower in group of patients treated with statins (the pooled relative risk 0.75 (95%CI, 0.65-0.87;  $p < 0.0001$ )) [24]. However, there is the lack of strong evidence to use statins for VTE prevention in clinical practice.

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