

Trombosi arteriosa degli arti inferiori e cancro

Background

- It has been established previously that deep venous thrombosis in the lower limb and pulmonary embolism may be presenting symptoms of cancer and are associated with a poor cancer prognosis.

VTE and OCCULT CANCER

- Unprovoked VTE may be the earliest sign of cancer
- Up to 10% of patients with unprovoked VTE receive a diagnosis of cancer in the year after their diagnosis of VTE
- More than 60% of occult cancers are diagnosed shortly after the diagnosis of unprovoked VTE
- Thereafter, the incidence rate of cancer diagnosis gradually declines and returns to the rate in the general population after 1 year.

Background

- However, whether arterial thromboembolism of the lower limb also can represent prodromal symptoms of occult cancer and worsen cancer prognosis has never been investigated.
- Despite similarities, the mechanisms of thrombus formation are fundamentally different in the venous versus arterial systems, preventing extrapolation of results from studies of venous thromboembolism.

Background

- A recent study examined the association between chronic intermittent claudication and cancer and reported increased long-term risk, presumably driven by smoking as a strong risk factor for both diseases.
- An acute thrombotic event such as lower limb arterial thrombosis may be linked to cancer through mechanisms other than shared risk factors.
 - First, an undiagnosed, yet active, cancer may induce a hypercoagulable and prothrombotic state, increasing the risk of arterial thrombosis.
 - Second, occult cancers may compress vessel walls of adjacent arteries supplying the lower limb. Hence, arterial thrombotic episodes in the lower limb may precede symptoms of malignancy.
- This would merit increased clinical attention and possible opportunistic screening for cancers in such patients.



Risk and Prognosis of Cancer After Lower Limb Arterial Thrombosis

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Aim

- To examine the risk of cancer overall and of site-specific cancers after a diagnosis of lower limb arterial thrombosis, compared with cancer risk in the general population.
- To assess the prognostic impact of previous lower limb arterial thrombosis on all-cause mortality after common cancers.

Methods

- Using nationwide population-based Danish medical registries, all patients diagnosed with first-time lower limb arterial thrombosis (1994–2013) were identified and followed until the occurrence of any subsequent cancer diagnosis, emigration, death, or November 30, 2013, whichever came first.
- Standardized incidence ratios with 95% confidence intervals were computed as the observed number of cancers relative to the expected number based on national incidence rates by sex, age, and calendar year.
- A matched comparison cohort of patients who had cancer without lower limb arterial thrombosis was constructed to examine the prognostic impact of lower limb arterial thrombosis on all-cause mortality after cancer.

Results

Characteristics of patients hospitalized with lower limb arterial thrombosis from 1994 to 2013 and members of the general population comparison cohort

	Lower Limb Arterial Thrombosis Cohort	Matched Comparison Cohort
Total	6600 (100)	131989 (100)
Median follow-up time, y (25th–75th percentiles)	2.7 (0.3–6.8)	6.7 (2.5–10.0)
Sex		
Female	3107 (47)	62 129 (47)
Male	3493 (53)	69 860 (53)
Median age, y (25th–75th percentiles)	71 (59–81)	
Age group		
0–29 y	146 (2)	2947 (2)
30–49 y	669 (10)	13 449 (10)
50–69 y	2313 (35)	46 065 (35)
≥70 y	3472 (53)	69 528 (53)
Calendar period		
1994–2003	3400 (52)	67 997 (52)
2004–2013	3200 (48)	63 992 (48)
Type of lower limb arterial thrombosis diagnosis		
Primary diagnosis	5320 (81)	–
Secondary diagnosis	1280 (19)	–

Comorbidities		
Myocardial infarction	1040 (16)	6898 (5)
Heart failure	1105 (17)	5988 (5)
Ischemic stroke	827 (13)	5978 (5)
Valvular heart disease	299 (5)	2415 (2)
Atrial fibrillation or atrial flutter	1430 (22)	7550 (6)
Aneurysmal disease in aorta or lower limb	512 (8)	785 (0.6)
Deep venous thrombosis	611 (9)	2022 (2)
Chronic pulmonary disease	841 (13)	7775 (6)
Chronic kidney disease	304 (5)	1487 (1)
Diabetes mellitus	814 (12)	6424 (5)
Obesity	265 (4)	2655 (2)
Intermittent arterial claudication	1110 (17)	1158 (1)
Alcoholism-related disorders	402 (6)	2482 (2)
Charlson Comorbidity Index score		
Low (score=0)	2277 (35)	94 147 (71)
Moderate (score=1–2)	3177 (48)	32 341 (25)
Severe (score >2)	1146 (17)	5501 (4)

Risk of any cancer in patients with lower limb arterial thrombosis in comparison with the general population

Follow-Up Interval	Incidence Rate per 1000 Person-Years (95% CI) in Patients With Lower Limb Arterial Thrombosis	Risk Time in Years for the Lower Limb Arterial Thrombosis Cohort	Incidence Rate per 1000 Person-Years (95% CI) in the Background Population	Observed/Expected*	Standardized Incidence Ratio (95% CI)
0–20 y	27.05 (25.14–28.96)	28538.9	20.08 (18.44–21.73)	772/573	1.35 (1.25–1.45)
0–6 mo	63.38 (53.65–73.11)	2571.8	19.34 (13.96–24.71)	163/50	3.28 (2.79–3.82)
7–12 mo	27.20 (20.37–34.02)	2242.8	19.09 (13.37–24.80)	61/43	1.42 (1.09–1.83)
0–365 days	46.53 (40.43–52.62)	4814.6	19.22 (15.30 - 23.14)	224/93	2.42 (2.11–2.76)
2–20 y	23.10 (21.16–25.03)	23724.3	20.26 (18.45–22.07)	548/481	1.14 (1.05–1.24)

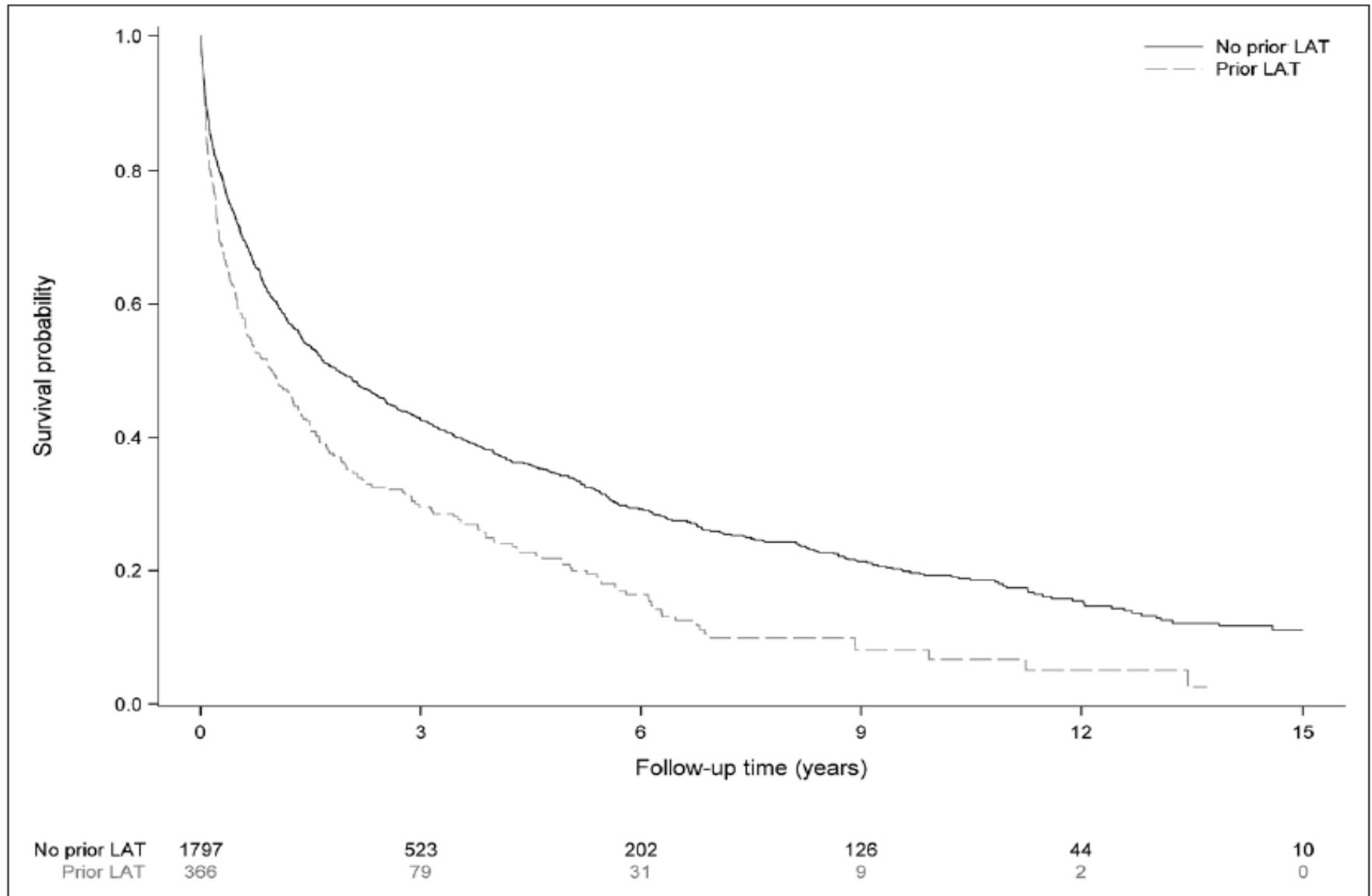
Risk of any cancer in patients with lower limb arterial thrombosis in comparison with a matched general population comparison cohort

Follow-Up Interval	Matched Comparison Cohort		Lower Limb Arterial Thrombosis Patients		Hazard Ratio Controlled for Matching Factors* (95% CI)
	Events	No. at Risk	Events	No. at risk	
0–20 y	20 115	131 989	772	6600	1.36 (1.26–1.46)
0–6 mo	1337	131 989	163	6600	3.30 (2.79–3.89)
7–12 mo	1217	124 760	61	4714	1.40 (1.08–1.81)
0–365 days	2562	131 989	224	6600	2.40 (2.09–2.76)
2–20 y	17 553	117 471	548	4304	1.15 (1.05–1.25)

Risk of selected site-specific cancers in patients with lower limb arterial thrombosis during 0 to 365 days of follow-up

	Incidence Rate per 1000 Person-Years (95% CI) in Patients With Lower Limb Arterial Thrombosis	Risk Time in Years for the Lower Limb Arterial Thrombosis Cohort	Incidence Rate per 1000 Person-Years (95% CI) in the Background Population	Observed/Expected	Standardized Incidence Ratio (95% CI)	Hazard Ratio Controlled for Matching Factors* (95% CI)
Smoking-related cancers						
Pancreas	3.53 (1.85–5.21)	4814.6	0.45 (0.00–1.06)	17/2	7.76 (4.52–12.43)	9.06 (5.10–16.08)
Lung	10.59 (7.69–13.50)	4814.6	2.01 (0.74–3.28)	51/10	5.26 (3.92–6.92)	5.39 (3.95–7.35)
Urinary bladder	2.91 (1.38–4.43)	4814.6	1.07 (0.15–2.00)	14/5	2.71 (1.48–4.55)	2.69 (1.54–4.70)
Other common cancers						
Colon	2.91 (1.38–4.43)	4814.6	1.53 (0.42–2.63)	14/7	1.90 (1.04–3.20)	1.84 (1.06–3.18)
Breast	3.12 (1.54–4.69)	4814.6	1.39 (0.34–2.44)	15/7	2.25 (1.26–3.70)	2.12 (1.25–3.62)
Prostate	2.28 (0.93–3.63)	4814.6	2.18 (0.86–3.50)	11/10	1.05 (0.52–1.88)	1.06 (0.58–1.95)
Nonmelanoma skin cancers	5.82 (3.66–7.97)	4814.6	4.58 (2.67–6.49)	28/22	1.27 (0.84–1.83)	1.25 (0.85–1.84)
Hematological cancers						
Leukemia	1.25 (0.25–2.24)	4814.6	0.41 (0.00–0.98)	6/2	3.06 (1.12–6.66)	3.18 (1.34–7.54)
Non-Hodgkin lymphoma	0.83 (0.02–1.64)	4814.6	0.45 (0.00–1.05)	4/2	1.85 (0.50–4.75)	2.38 (0.84–6.71)
Metastasis and unspecified cancer in lymph nodes (only in the absence of a coded primary tumor)	3.12 (1.54–4.69)	4814.6	0.44 (0.00–1.04)	15/2	7.05 (3.94–11.63)	7.52 (4.15–13.64)

Survival curve for patients who have cancer with and without lower limb arterial thrombosis



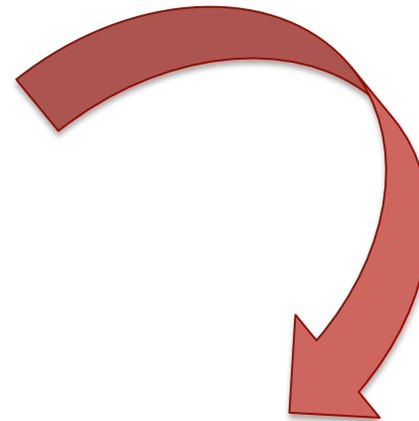
Conclusions

- Lower limb arterial thrombosis was a marker of increased risk of cancer, in particular in the short term and most pronounced for smoking-related cancers.
- In addition, lower limb arterial thrombosis was an adverse prognostic factor for all-cause mortality in patients with colon, lung, urinary bladder, and breast cancer, but not prostate cancer.
- The potential to herald a clinically silent, but preexisting, cancer merits increased attention to symptoms or signs pointing to a potential cancer when patients present with lower limb arterial thrombosis.

Clinical Perspective

What Is New?

- Venous thromboembolism can be a presenting symptom of cancer and an adverse prognostic factor for patients with cancer; however, it remains unknown whether a thrombus in the arterial system of the lower limb is also a marker of increased cancer risk and poor cancer outcome.
- In a nationwide population-based cohort including 6600 patients with lower limb arterial thrombosis, the risk of any cancer was increased in comparison with the general population, especially during the first 6 months of follow-up.
- Lower limb arterial thrombosis was also an adverse prognostic factor for mortality in common cancers.



What Are the Clinical Implications?

- Patients presenting with lower limb arterial thrombosis potentially may harbor a clinically silent cancer.
- Based on our findings, opportunistic screening focused on cancer-related symptoms and signs during diagnostic workup for lower limb arterial thrombosis seems prudent.
- It remains unknown whether patients with lower limb arterial thrombosis may gain prognostic benefit from a formalized screening program to detect cancers at an earlier stage.