

# 2<sup>ND</sup> GESCAT SYMPOSIUM

CAT - How to Improve Results  
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18<sup>th</sup> - 19<sup>th</sup>  
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HF IPANEMA PARK PORTO

Arterial Thrombosis in  
Cancer Patients  
- is it still an underestimated  
complication?

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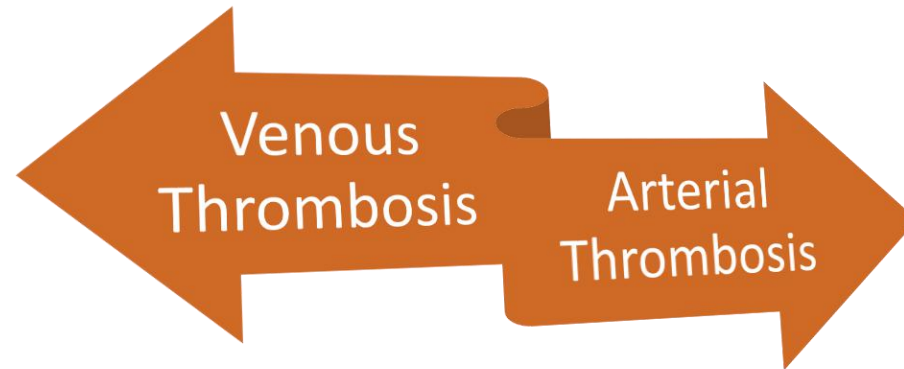
Diretora de Serviço: Dra. Maria Emília Ferreira

# Arterial Thrombosis in Cancer Patients

- is it still an underestimated complication?

With newer and more effective treatments, many patients live for years or even decades after an initial cancer diagnosis

Patients with cancer experience a high burden of thromboembolic disease



Cancer patients receiving outpatient chemotherapy -> arterial thrombosis accounted for 5.6% of deaths

## Epidemiology

### Arterial Thrombosis:

- Arterial thromboembolic events
- MI
- Stroke

*J Am Coll Cardiol.* 2017 Aug 22;70(8):926-938. doi: 10.1016/j.jacc.2017.06.047.

### **Risk of Arterial Thromboembolism in Patients With Cancer.**

Navi BB<sup>1</sup>, Reiner AS<sup>2</sup>, Kamel H<sup>3</sup>, Iadecola C<sup>3</sup>, Okin PM<sup>4</sup>, Elkind MSV<sup>5</sup>, Panageas KS<sup>2</sup>, DeAngelis LM<sup>6</sup>.

Incidence of ATE at 6 months was 4.7% in all cancer patients compared to 2.2% in the matched control cohort

Patients with lung, gastric, or pancreatic cancers had the highest rates of ATE (8.3, 6.5, and 5.9%, respectively)

Ischemic stroke was less common in cancer patients than myocardial infarction (2.0% at 6 month follow-up versus 3.0% respectively)

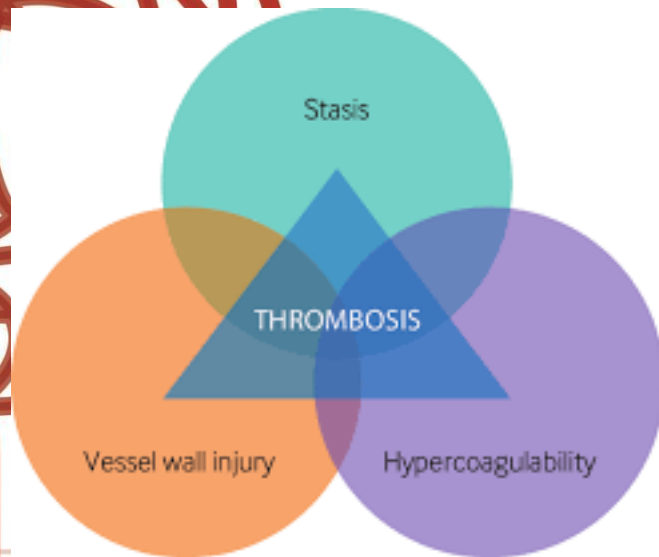
Advanced stage of cancer was associated with a significant increase in ATE (stage 0 2.3% incidence at 6 months compared to 7.7% for stage 4)

ATE was associated with increased mortality even after matching for all factors and the stage of the cancer (hazard ratio 3.1, CI 3.0–3.1)

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## Risk Factors



Platelet activation in the setting of preexisting disease, such as atherosclerosis and vasculitis, appears to be crucial for the development of arterial thrombosis

Many risk factors, such as **age**, **smoking**, **hypertension**, and **diabetes**, are common to both venous and arterial thrombi

Case reports of patients presenting with arterial thrombosis as the first sign of an occult malignancy or progression of an early-stage cancer



**Cancer** may be an independent risk factor for arterial thrombi

**Radiation** is a common part of cancer treatment and an important modifier of arterial thrombosis risk

**Chemotherapy**

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## Risk Factors

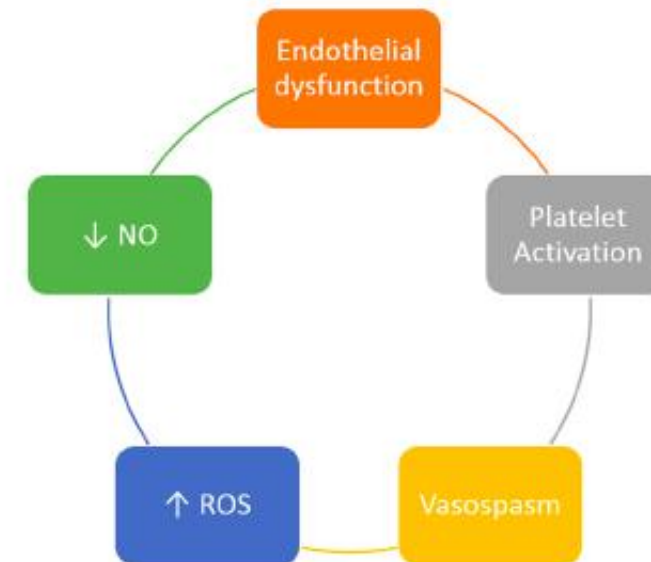
### Chemotherapy-related arterial thrombosis

*Curr Atheroscler Rep.* 2018 Feb 8;20(2):10. doi: 10.1007/s11883-018-0702-5.

#### Chemotherapeutic Agents and the Risk of Ischemia and Arterial Thrombosis.

Hassan SA<sup>1</sup>, Palaskas N<sup>2</sup>, Kim P<sup>2</sup>, Iliescu C<sup>2</sup>, Lopez-Mattei J<sup>2</sup>, Mouhayar E<sup>2</sup>, Mougdil R<sup>2</sup>, Thompson K<sup>2</sup>, Banchs J<sup>2</sup>, Yusuf SW<sup>2</sup>.

Angiogenesis inhibitors, alkylating agents, antimetabolites, antimicrotubules and proteasome inhibitors can lead to ischemic complications in patients with cancer

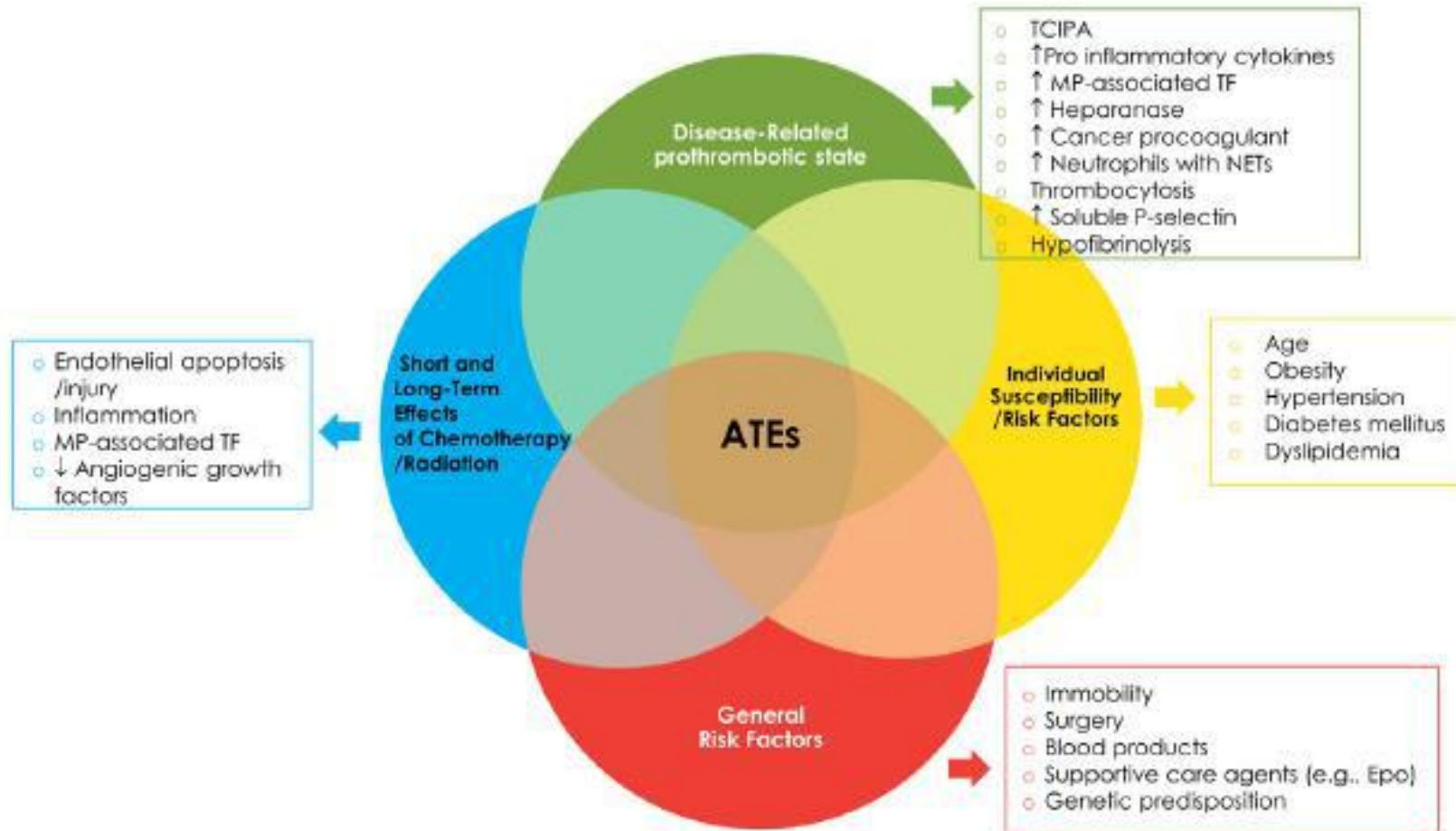


Chemotherapeutic Agent	Potential Mechanism(s)
Angiogenesis Inhibitors	Endothelial dysfunction Platelet activation ↓NO + ↑ROS
Antimetabolites	Vasospasm
Alkylating agents	Endothelial dysfunction
Antimicrotubules	Vasospasm

Pathophysiology

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## Pathophysiology

### Specific cancers with increased risk for arterial thrombotic events

#### Solid Tumors

The risk of ATE varied by cancer type, with **lung**, **gastric**, and **pancreatic** cancers conferring the highest risk

ATE portended adverse prognosis, with a 3-fold increased mortality

#### Myeloproliferative disorders

Myeloproliferative neoplasms, particularly **polycythemia vera** and **essential thrombocythemia**, are associated with increased thrombosis rates, with arterial events accounting for 60%–70% of all thrombotic events

**Age**, **leukocytosis** (above  $15 \times 10^9/L$ ) and a **history of thrombosis** have been associated with arterial thrombosis in MPN

Low-dose aspirin (75 to 100 mg/day) is used for the primary prevention of thrombosis in patients with PV or ET, and reduces the combined endpoint of nonfatal acute myocardial infarction, nonfatal stroke, or death from cardiovascular causes in PV by 60%

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## Pathophysiology

### Specific cancers with increased risk for arterial thrombotic events

#### Acute promyelocytic leukemia

Severe coagulopathy

The incidence of thrombotic events in APL was low prior to the introduction of all-trans-retinoic acid (ATRA)

ATRA therapy rapidly improves bleeding risk, but may favor the development of thrombotic events due to changes in the balance between procoagulant and fibrinolytic properties of promyelocytes



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## Clinical Features

### Arterial Thrombosis:

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- Stroke

*Curr Treat Options Cardiovasc Med.* 2018 Apr 7;20(5):40. doi: 10.1007/s11936-018-0635-x.

### Arterial Thrombosis in Patients with Cancer.

Tuzovic M<sup>1</sup>, Herrmann J<sup>2</sup>, Iliescu C<sup>3</sup>, Marmagkiolis K<sup>4</sup>, Ziaeiian B<sup>1</sup>, Yang EH<sup>5</sup>.

The typical symptoms depend on the affected organ: **chest pain for CAD, limb pain for PAD, or neurologic deficits for stroke**

The overall diagnostic and treatment strategies center on the goal to restore blood flow as soon as possible

**Type II MI** (ischemia due to either increased oxygen demand or decreased supply) Vs **type I**



aspirin can be given if the platelet count is >10000 and DAPT with aspirin and clopidogrel is reasonable for platelet counts between 30 and 50000; ticagrelor caution <50000

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### **Arterial Thrombosis in Patients with Cancer.**

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**Revascularization** is imperative in the setting of critical ischemia or infarction

Treatment options include:

- thrombectomy (as in the case of PAD or stroke)
- percutaneous coronary intervention
- bypass surgery
- percutaneous peripheral angioplasty

## Clinical Features

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*Blood*. 2019 Feb 21;133(8):781-789. doi: 10.1182/blood-2018-06-860874. Epub 2018 Dec 21.

### Arterial thromboembolic events preceding the diagnosis of cancer in older persons.

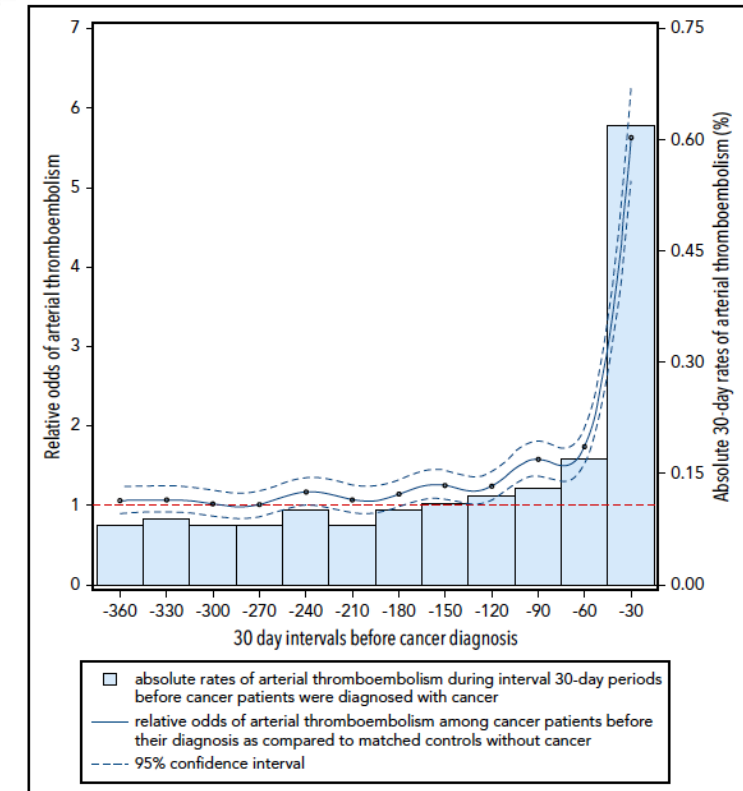
Navi BB<sup>1,2,3</sup>, Reiner AS<sup>1</sup>, Kamel H<sup>1,2</sup>, Iadecola C<sup>1,2</sup>, Okin PM<sup>4</sup>, Tagawa ST<sup>5</sup>, Panageas KS<sup>6</sup>, DeAngelis LM<sup>1,2,3</sup>.

10% of venous thromboembolism may be associated with occult cancer

In the 360 days before a cancer diagnosis, the risk of an arterial thromboembolic event was increased nearly 70%

This risk first became increased about 5 months before cancer diagnosis and thereafter progressively rose until **peaking in the month before cancer diagnosis**, when the risk was increased more than **fivefold**

These data suggest that some myocardial infarction and ischemic stroke events may be triggered, or potentially caused by, occult cancer



## Clinical Features

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Vascular. 2015 Feb;23(1):55-61. doi: 10.1177/1708538114537048. Epub 2014 May 21.

### **Acute limb ischemia in cancer patients: aggressive treatment is justified.**

Silverberg D<sup>1</sup>, Yalon T<sup>2</sup>, Reinitz ER<sup>2</sup>, Yakubovitch D<sup>2</sup>, Segev T<sup>2</sup>, Halak M<sup>2</sup>.

Of 147 patients treated for ALI (122 lower extremity, 25 upper extremity), 24 (16%) were cancer patients. Mean follow-up was 9.8 months for the malignancy group and 13.4 months for the control.

Perioperative mortality rates were similar among cancer and non-cancer patients (20% vs. 16%, respectively, NS)

Freedom from major amputation at 30 months was similar (95% vs. 89%, NS)

Treatment of ALI among cancer patients can be achieved with perioperative mortality and limb salvage rates comparable to non-cancer patients. Aggressive treatment is justified when treating cancer patients with ALI

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## Conclusion

Arterial thrombosis complicating cancer and cancer chemotherapy are common and have increased in parallel with the expanding armamentarium of novel chemotherapeutic agents

Improved survival led to cardiovascular complications becoming clinically relevant many years after cancer diagnosis

Data show that some myocardial infarction, ischemic stroke and acute limb ischemia events may be triggered, or potentially caused by, **occult cancer**



Future research is needed to identify clinically useful biomarkers for occult cancer in patients with arterial thromboembolic events and to determine the utility of cancer screening strategies in these patients, particularly among those with cancer risk factors or unexplained “cryptogenic” events

Prevention and treatment of cancer-associated arterial thrombosis may be improved by **greater awareness** and **careful monitoring for vascular toxicity**, aggressive efforts to **optimize conventional cardiovascular risk factors**, and **use of antiplatelet and antithrombotic agents in selected patients**. These issues are targets for future studies aimed to reduce arterial thrombosis in patients with cancer