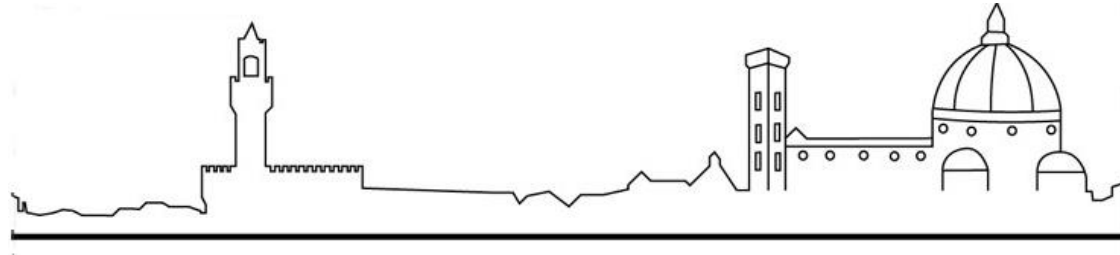


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Thrombosis – causative factors and preventative measures

Fulvio Pinelli, MD
Careggi University Hospital
Florence, Italy

Catheter-related thrombosis

Definition

CRT = Appearance of a thrombus on the vascular wall, most frequently where the endothelium is damaged by the catheter introduction site and/or where the contact between vein wall and catheter is maximal.

Catheter-related thrombosis

Definition

Management of occlusion and thrombosis associated with long-term indwelling central venous catheters

Jacquelyn L Baskin, Ching-Hon Pui, Ulrike Reiss, Judith A Wilimas, Monika L Metzger, Raul C Ribeiro, Scott C Howard

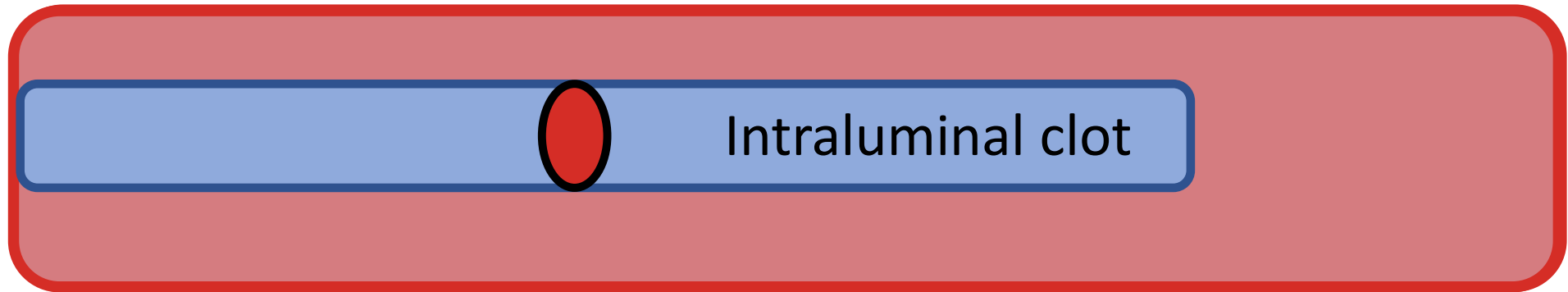
Long-term central venous catheters (CVCs) are important instruments in the care of patients with chronic illnesses, but catheter occlusions and catheter-related thromboses are common complications that can result from their use. In this Review, we summarise management of these complications. Mechanical CVC occlusions need cause-specific treatment, whereas thrombotic occlusions usually resolve with thrombolytic treatment, such as alteplase. Prophylaxis with thrombolytic flushes might prevent CVC infections and catheter-related thromboses, but confirmatory studies and cost-effectiveness analysis of this approach are needed. Risk factors for catheter-related thromboses include previous catheter infections, malposition of the catheter tip, and prothrombotic states. Catheter-related thromboses can lead to catheter infection, pulmonary embolism, and post-thrombotic syndrome. Catheter-related thromboses are usually diagnosed by Doppler ultrasonography or venography and treated with anticoagulation therapy for 6 weeks to a year, dependent on the extent of the thrombus, response to initial therapy, and whether thrombophilic factors persist. Prevention of catheter-related thromboses includes proper positioning of the CVC and prevention of infections; anticoagulation prophylaxis is not currently recommended.

Lancet 2009; 374: 159–69

Department of Oncology and International Outreach Program (J L Baskin MD, Prof C-H Pui MD, J A Wilimas MD, M L Metzger MD, R C Ribeiro MD, S C Howard MD), and Department of Hematology (U Reiss MD), St Jude Children's Research Hospital, Memphis, TN, USA; Department of Hematology and Oncology, Children's Hospital of Los Angeles, Los Angeles, CA, USA (J L Baskin); and

Catheter-related thrombosis

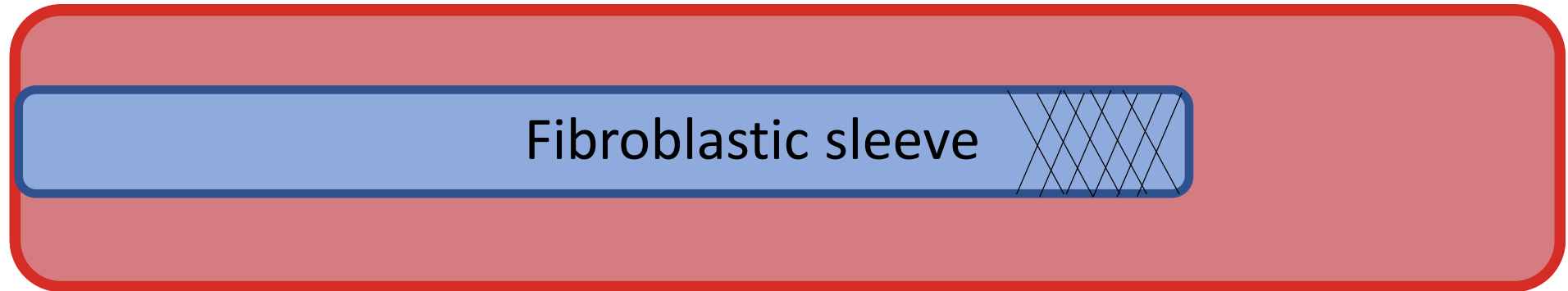
Definition



Intraluminal clot is not CRT

Catheter-related thrombosis

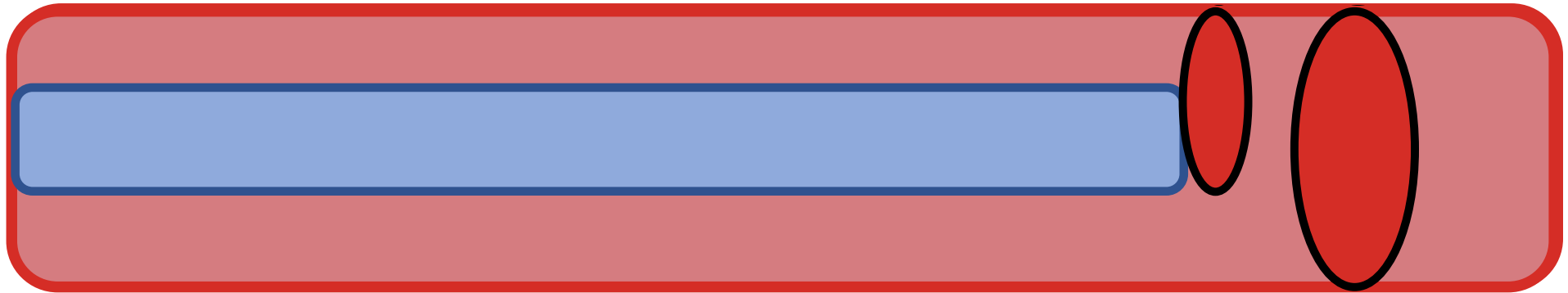
Definition



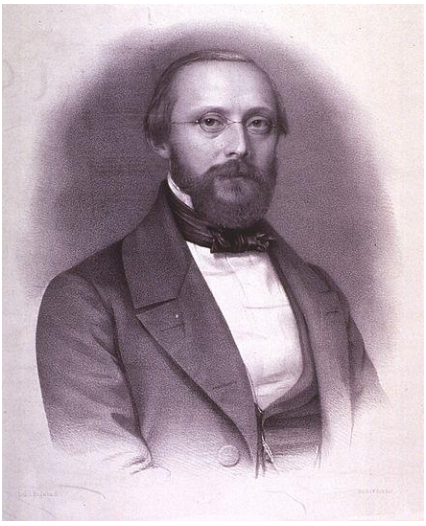
Fibroblastic sleeve is not CRT

Catheter-related thrombosis

Definition



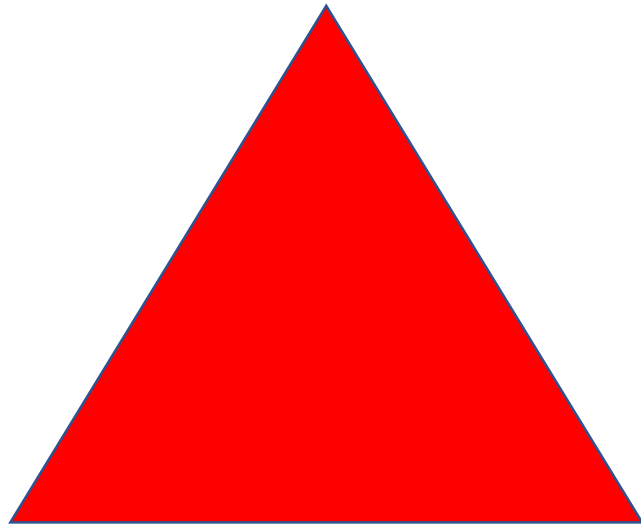
Mural and venous thrombosis are CRT



Pathophysiology: the Virchow's Triade

ENDOTHELIAL DAMAGE

Catheter insertion



Rudolf Virchow
(1821-1902)

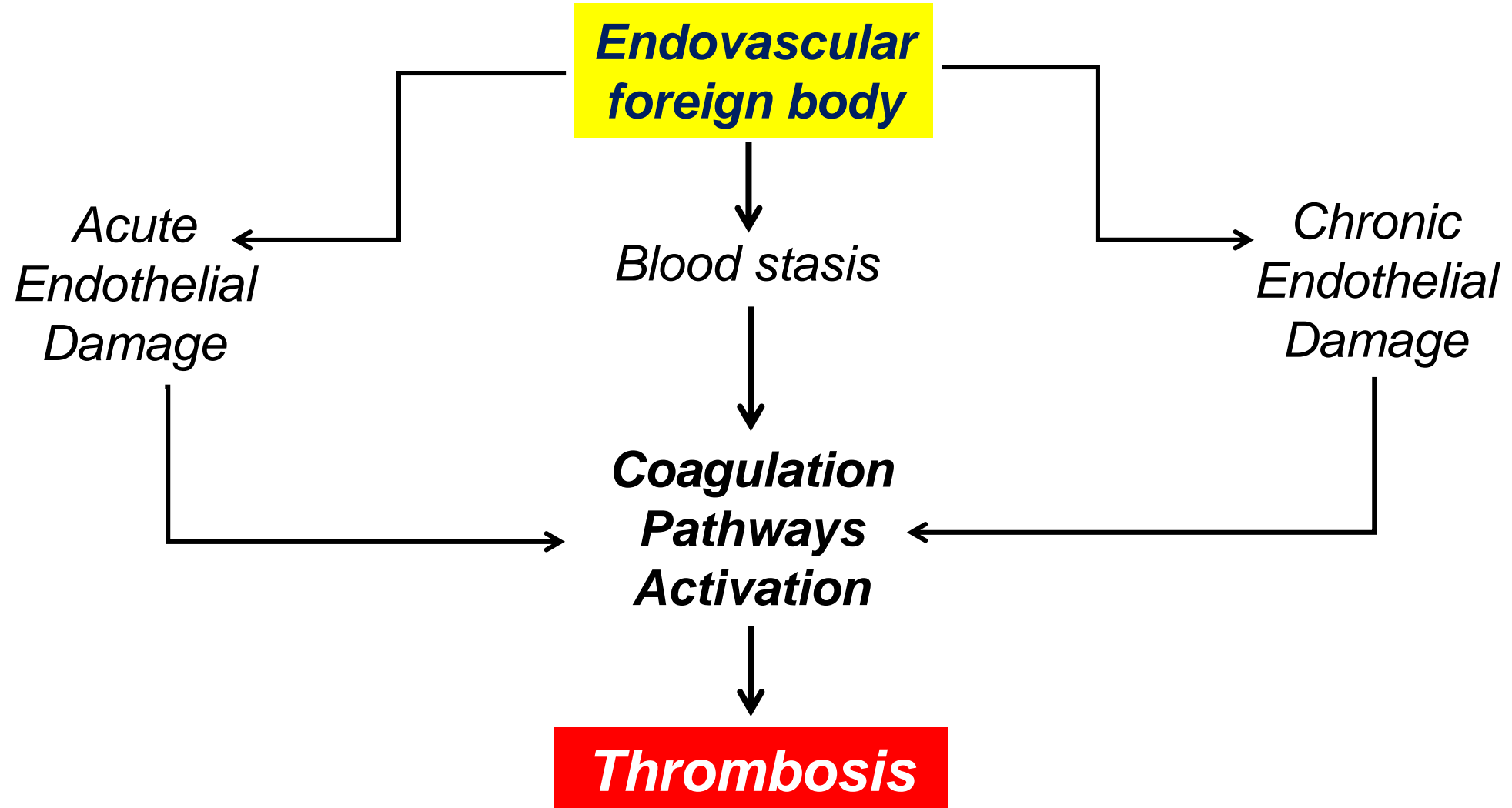
HYPERCOAGULABILITY

- Sepsis
- Malignancies
- Inflammation
- Thrombophilia

BLOOD STASIS

- Presence of the catheter itself
- Infusion fluids: CHT, viscous drugs, TPN, etc.
- Immobilization

Pathophysiology



Catheter-related thrombosis natural history in adult patients: a tale of controversies, misconceptions, and fears

Fulvio Pinelli and Paolo Balsorano 

Majority of CRT precocious
(within 2 weeks from
implantation)

Approximately 1/4
symptomatic events

Treated with
uncommon
consequences

Natural history of CRT

Approximately 3/4
asymptomatic events

Uncommon Long-term
sequelae without
treatment



Which are the risk factors for CRT ?

- Choice of the device
- Patients' predisposing factors
- Technique of insertion
 - Catheter/vein ratio
 - Magnitude of the trauma to the vein wall
 - Position of the tip

Choice Of The Device

Is there any clinical evidence that some type of central venous approach (**CICC** vs. **PICC** vs. **FICC**) may actually reduce the risk of CRT ?

Are **FICC** particularly at risk of CRT ?

- Yes
- Much evidence shows that Femorally Inserted Central Catheters are at increased risk of CRT (**5-15%** in adult patients)
- Lower limb CRT is also associated with a **four fold increase** of risk of pulmonary embolism (Minet 2015)

Are **CICC** particularly at risk of CRT ?

- It depends on the caliber, the route and the technique of insertion:
 - Larger catheters (dialysis) = more risk
 - Supraclavicular route = more risk
 - Ultrasound guided puncture = less risk
- No hard data about the actual incidence, probably less than **3-5%**
- Risk of PE is low but not irrelevant

Are **PICC** particularly at risk of CRT ?

Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis

Vineet Chopra, Sarah Anand, Andy Hickner, Michael Buist, Mary A M Rogers, Sanjay Saint, Scott A Flanders

Chopra V et Al. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis.

Lancet. 2013;382:311-25

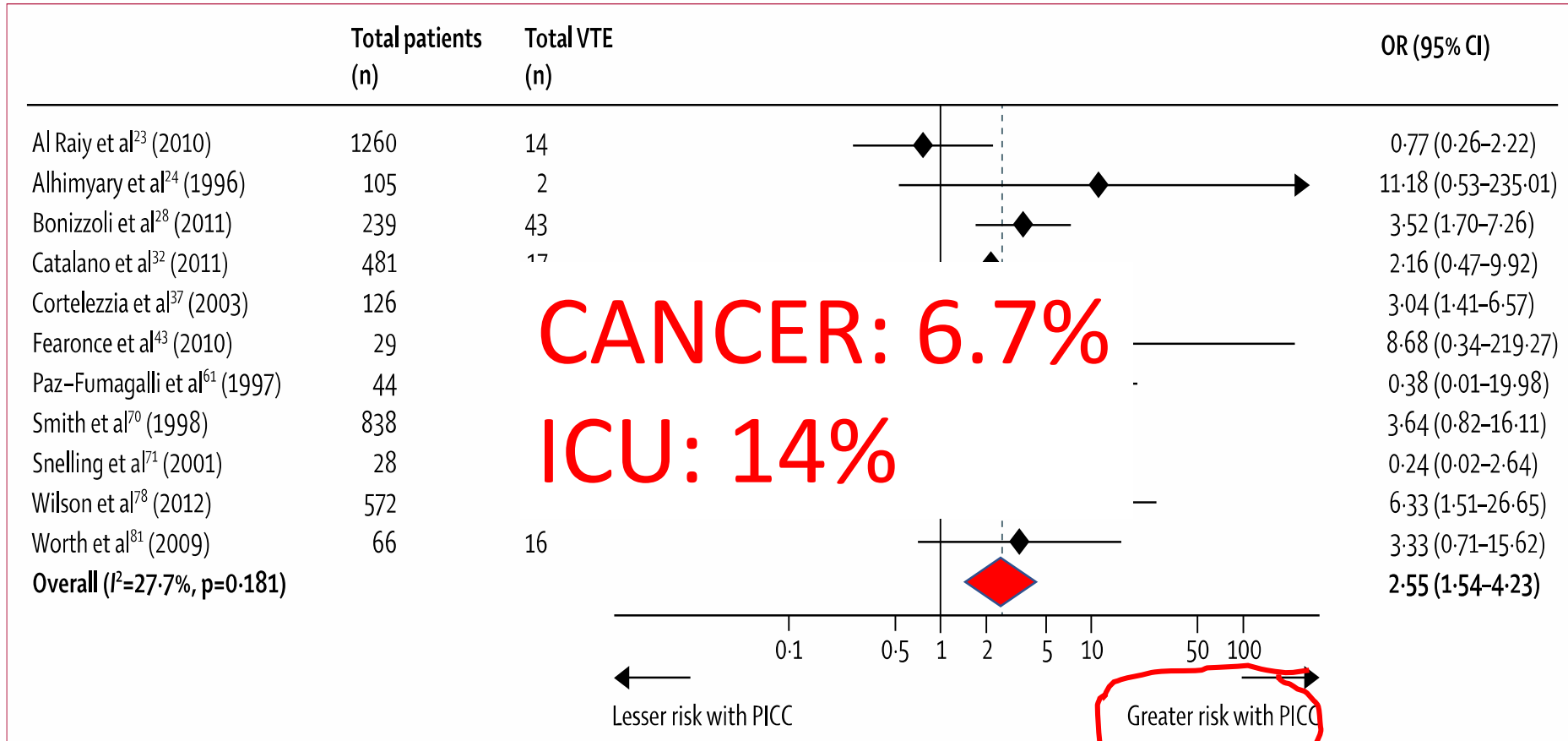


Figure 4: Risk of venous thromboembolism between peripherally inserted central catheters and central venous catheters in studies with a comparison group Forest plot showing odds of development of upper-extremity DVT in patients with peripherally inserted central catheters versus central venous catheters. VTE=venous thromboembolism. OR=odds ratio. PICC=peripherally inserted central catheter.

Chopra V et Al. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis.

Lancet. 2013;382:311-25

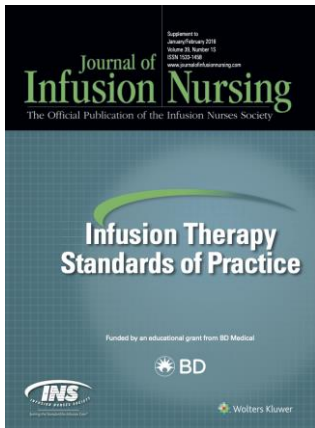
64 studies included, only 9 to be taken into consideration

- Many studies considered asymptomatic CRT
- Some were performed without the use of ultrasound;
- Same catheter size was used in all patients, regardless of the vein caliber;
- Many studies were retrospective;
- In many studies: tip position SVC;
- In some studies PICC were placed at antecubital fossa, paretic arm, etc.

The Michigan Appropriateness Guide for Intravenous Catheters (MAGIC): Results From a Multispecialty Panel Using the RAND/UCLA Appropriateness Method

Vineet Chopra, MD, MSc; Scott A. Flanders, MD; Sanjay Saint, MD, MPH; Scott C. Woller, MD; Naomi P. O'Grady, MD; Nasia Safdar, MD, PhD; Scott O. Trerotola, MD; Rajiv Saran, MD, PhD; Nancy Moureau, BSN, RN; Stephen Wiseman, PharmD; Mauro Pittiruti, MD; Elie A. Akl, MD, MPH, PhD; Agnes Y. Lee, MD, MSc; Anthony Courey, MD; Lakshmi Swaminathan, MD; Jack LeDonne, MD; Carol Becker, MHSA; Sarah L. Krein, PhD, RN; and Steven J. Bernstein, MD, MPH

ment (13, 14). In addition, PICCs are associated with morbid complications, including venous thromboembolism and central line-associated bloodstream infection (15-17). Ensuring appropriate use of PICCs is thus vital to preventing these costly and potentially fatal adverse events.



INS 2016

Use a PICC with caution in patients who have cancer or are critically ill due to venous thrombosis and infection risk.^{19,20} (III)

19. Chopra V, Anand S, Hickner A, et al. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systemic review and meta-analysis. *Lancet*. 2013;382(9889): 311-325.
20. Chopra V, O'Horo J, Rogers M, et al. The risk of bloodstream infection associated with peripherally inserted central catheters compared with central venous catheters in adults: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol*. 2013;34(9):908-918.

Peripherally inserted central catheter–related thrombosis rate in modern vascular access era—when insertion technique matters: A systematic review and meta-analysis

Paolo Balsorano¹, Gianni Virgili², Gianluca Villa³, Mauro Pittiruti⁴, Stefano Romagnoli¹, Angelo Raffaele De Gaudio³ and Fulvio Pinelli¹

- 2010-2018
- 15 studies

Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis

Vineet Chopra, Sarah Anand, Andy Hickner, Michael Buist, Mary A M Rogers, Sanjay Saint, Scott A Flanders



PICC-related thrombosis rate in modern vascular access era: when insertion technique matters. A systematic review and meta-analysis

Paolo [Balsorano](#), MD¹; Prof. Gianni [Virgili](#)²; [Gianluca Villa](#), MD, PhD³; Mauro [Pittiruti](#), MD⁴; Stefano [Romagnoli](#), MD, PhD¹; Prof. Angelo Raffaele De Gaudio³; [Fulvio Pinelli](#), MD¹

Retrospective and Prospective

No insertion info

No tip location info info

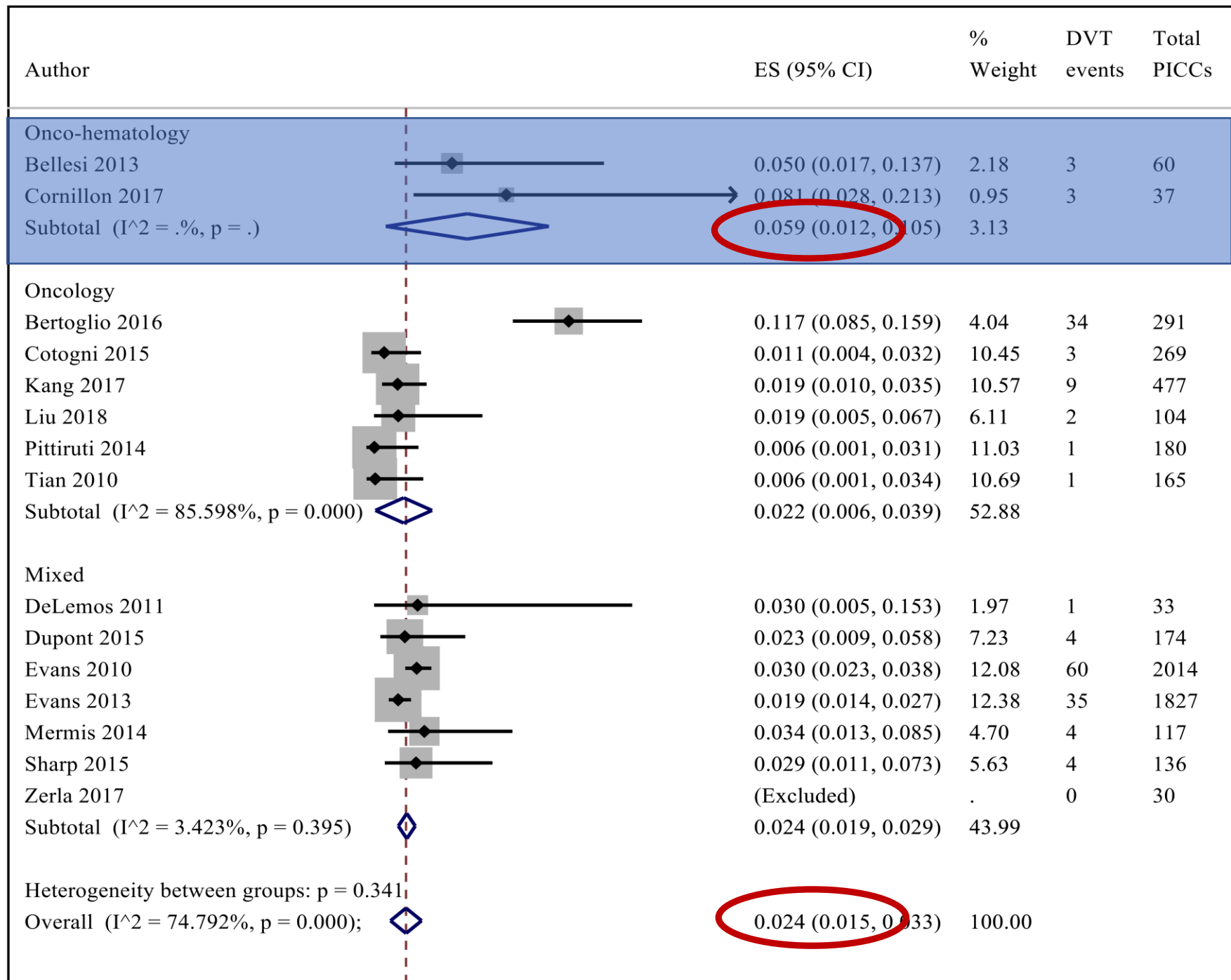
Symptomatic and
Asymptomatic

Only prospective

Insertion bundle

Tip location verified

Only symptomatic



So, incidence of CRT for PICCs is around **2.4%**.
What about other VADs in cancer patients?

CRT in cancer patients with **ports**:

3.8 % (Decousus 2018)

2.3 % (Hong 2018)

Risk of Thrombosis

There is no clear evidence-based difference between CICC and PICCs.

Though, PICC have a higher risk of thrombosis:

- In ICU hematologic patients (leukemia)
- When PICCs are inserted in veins which are too small for the ideal catheter/vein ratio
- When PICCs are inserted without a proper insertion protocol

Are **PICC** particularly at risk of CRT ?

- Current evidence shows that **if PICCs are inserted respecting the proper indications/contraindications and paying attention to the catheter/vein caliber and to the tip position**, the expected rate of CRT is **3%** or less in both oncologic and non-oncologic patients, and somehow higher (**5-6%**) in hematologic patients.
- The risk of pulmonary embolism is minimal or absent.

CRT risk vs. PICC advantages

- Even in populations with the highest thrombotic risk (hematology pts), the benefits of PICCs outnumber the risk of CRT
 - No insertion-related complications
 - Safe insertion even in severe coagulopathy
 - Safe insertion in severe cardiorespiratory disease
 - Low risk of CRBSI
 - Easy removal, easy replacement

CICC, PICC or FICC ?

- Estimated risk of symptomatic CRT
 - **CICC** **0-2 %** **low risk of pulmonary embolism**
 - **PICC** **0-5 %** **no risk of pulmonary embolism**
 - **FICC** **5-15 %** **high risk of pulmonary embolism**

In terms of prevention of thrombosis-related morbidity/mortality, the use of PICCs should be recommended over CICCs and FICCs

Choice of the Material

Silicone and II and III generation PUR catheters are less thrombogenic than polyethylene or PVC ones.

- short peripheral cannulas (PFTE>PUR)
- long peripheral cannulas (PE>PUR)
- Midlines, PICC, CICC: PUR = silicone

Choice of The Material

Is there any evidence that any material treated with specific substances may reduce thrombotic risk?

NO.

PICC with treated PUR

- PICC with Endexo technology – effect on CRT: n.s.
 - Kleidon (RCT, pediatrics, 2018)
- PICC with CHG treatment – effect on CRT: none
- PICC with CHG treatment – effect on fibroblastic sleeve
 - Sylvia 2018 (ovine model)

Patient's Predisposing Factors

Is there anything we can do about patients' predisposing factors?

Catheter-Related Central Venous Thrombosis: The Development of a Nationwide Consensus Paper in Italy

**GAVeCeLT Consensus
JAVA 2007**

*Costantino Campisi, MD, Roberto Biffi, MD, and Mauro Pittiruti, MD
on behalf of the GAVeCeLT Committee for the Consensus*

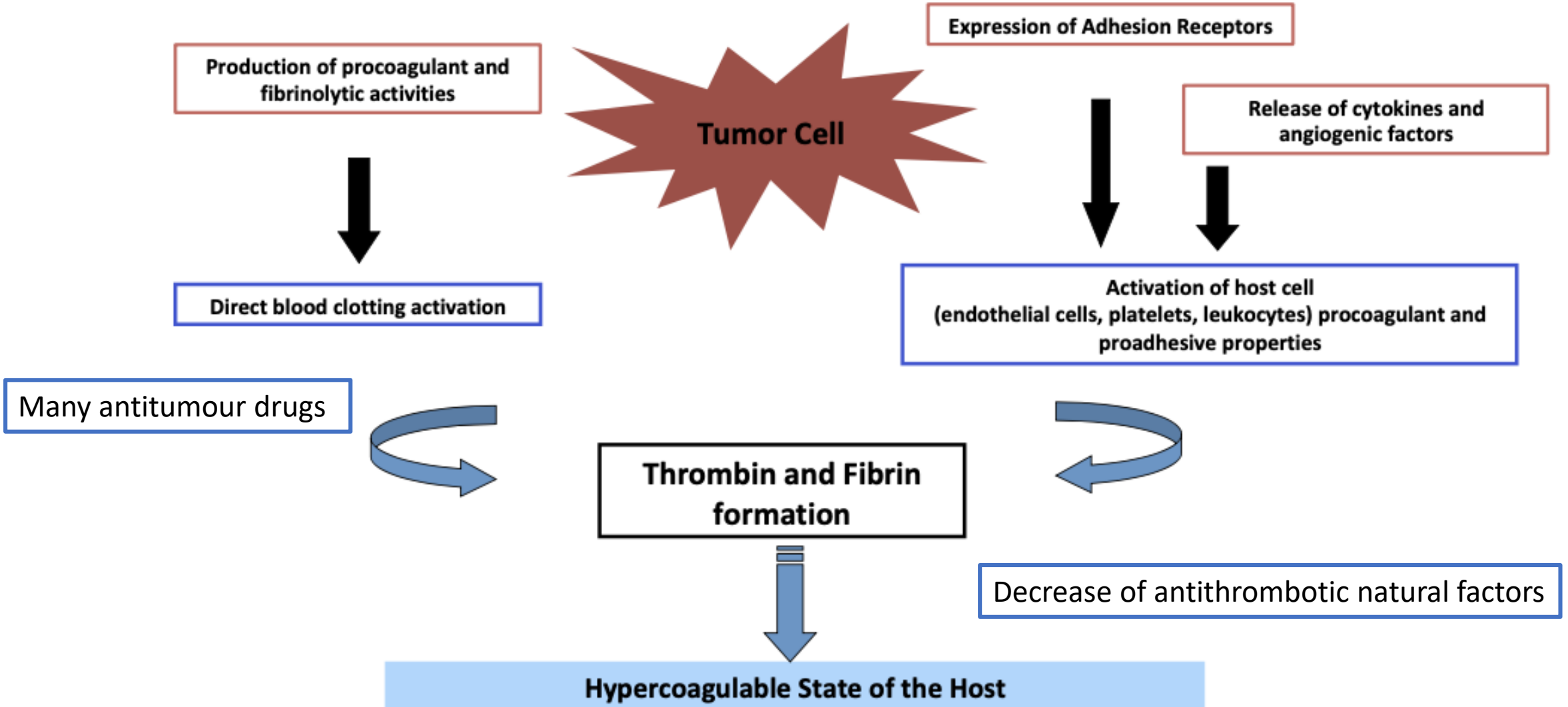
Q4

Which are the patients' risk factors?

Neoplastic disease and chemotherapy are recognised risk factors for development of deep vein thrombosis in patients bearing a central venous catheter.

Pathophysiology is known, it includes direct release of thrombogenic factors by neoplastic cells, decrease of antithrombotic natural factors induced by tumour, and the procoagulant activity of many antitumour drugs.

TUMOR CELL-DEPENDENT MECHANISMS OF BLOOD CLOTTING ACTIVATION



Not all cancer patients have the same risk

Patient characteristics	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma , gynecologic, bladder, testicula)	1
Pre-CT platelet count > 350,000/ml	1
Hemoglobin level >10 g/dL or use of erythropoietin stimulating agents	1
Pre-CT leukocyte count > 11*10⁹/L	1
BMI > 35 Kg/m²	1

Should we use pharmacological prophylaxis in oncologic patients with VAD?



CHEST

Supplement

ANTITHROMBOTIC AND THROMBOLYTIC THERAPY 8TH ED: ACCP GUIDELINES

Executive Summary*

American College of Chest Physicians
Evidence-Based Clinical Practice Guidelines
(8th Edition)

7.0.3. For cancer patients with indwelling central venous catheters, we recommend that clinicians not use either prophylactic doses of LMWH (Grade 1B). or minidose warfarin (Grade 1B) to try to prevent catheter-related thrombosis.

Should we use routine pharmacological prophylaxis in some patients with VAD ?



Catheter-Related Central Venous Thrombosis: The Development of a Nationwide Consensus Paper in Italy

*Costantino Campisi, MD, Roberto Biffi, MD, and Mauro Pittiruti, MD
on behalf of the GAVeCeLT Committee for the Consensus*

**GAVeCeLT Consensus
JAVA 2007**

Current recommendations

- Pharmacological prevention
 - Only with LMWH (100 U/kg/24h)
 - Only in high-risk patients
 - Hereditary anomalies associated with thrombophilia
 - Previous catheter-related venous thrombosis
 - Previous DVT related to the neoplastic disease

Patient's predisposing Factors

Risk is increased in ICU patients

REVIEW

Open Access



Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis

Clémence Minet^{1*}, Leila Potton¹, Agnès Bonadona¹, Rébecca Hamidfar-Roy¹, Claire Ara Somohano¹, Maxime Lugosi¹, Jean-Charles Cartier¹, Gilbert Ferretti^{2,3}, Carole Schwebel¹ and Jean-François Timsit^{1,3}

In particular:

- Sedated and ventilated patients
- Sepsis
- Vasopressors
- FICC
- VAD inserted in emergency

Catheter-Related Central Venous Thrombosis: The Development of a Nationwide Consensus Paper in Italy

**GAVeCeLT Consensus
JAVA 2007**

*Costantino Campisi, MD, Roberto Biffi, MD, and Mauro Pittiruti, MD
on behalf of the GAVeCeLT Committee for the Consensus*

Q4

Which are the patients' risk factors?

In prospective studies, **mutations of Factor V Leiden** and/or **prothrombin gene** have been found to be related to an higher incidence of central venous thrombosis in cancer patients bearing a central venous catheter.

Screening procedures have not been proven to be cost-effective.

May be clinically useful to quantify the patient's risk of CRT ?

NO.

Example: Michigan Risk Score

Michigan Risk Score for PICC-Related Thrombosis

Predicts risk of DVT in patients with peripherally inserted central catheter (PICC).

IMPORTANT

This calculator is not yet externally validated and should therefore be used with caution.

INSTRUCTIONS

Use in patients ≥ 18 years old admitted to a medical service (i.e., not surgical). Do not use in pregnant patients.

Example: Michigan Risk Score

Another central venous catheter present At the time of index PICC placement	No 0	Yes +1	
WBC $>12.0 \times 10^9/\mu\text{L}$ At the time of index PICC placement	No 0	Yes +1	
Number of PICC lumens	1 0	2 +1	3-4 +2
History of VTE	Never 0	Yes, >30 days prior +2	Yes, within 30 days +3
Active cancer On chemotherapy or admitted for cancer-related reasons	No 0	Yes +3	

10 points

Class IV

High risk

4.7 %

Probability of VTE if PICC inserted

Copy Results 

Next Steps 

Example: Michigan Risk Score

- **Worst scenario:**

- Patient has already a central line
- WBC > 12,000
- We need a 3-lumen PICC
- History of VTE in the last 30 days
- History of active cancer

Example: Michigan Risk Score

- **Worst scenario:**

- Patient has already a central line
- WBC > 12,000
- We need a 3-lumen PICC
- History of VTE in the last 30 days
- History of active cancer

10 points = Class IV = 4.7% risk of CRT

Example: Michigan Risk Score

- Now we know that the risk of PICC related thrombosis is 4.7 %

Example: Michigan Risk Score

- Now we know that the risk of PICC related thrombosis is 4.7 %
- **And now?**

Example: Michigan Risk Score

- Now we know that the risk of PICC related thrombosis is 4.7 %
- **And now?**
- **If the patient needs a central line and there are no technical contraindication to a PICC, I will insert a PICC anyway**

Example: Michigan Risk Score

- Now we know that the risk of PICC related thrombosis is 4.7 %
- **And now?**
- **If the patient needs a central line and there are no technical contraindication to a PICC, i will insert a PICC anyway**
- **Remember: PICC-related thrombosis is a low cost complication with low morbidity and zero mortality**

Role of technique insertion

The best prevention: a proper technique of VAD insertion

1. Consider the catheter/vein ratio
2. Minimize the vein trauma
3. Assess a proper position of the tip
4. Stabilize the catheter

i.e: USE an INSERTION BUNDLE FOR CRT PREVENTION (ex. **GAVeCeLT bundle**)

The **GAVeCeLT insertion bundle** for preventing CRT

1. Appropriate choice of the vein
2. Appropriate technique of venipuncture
3. Adequate position of the tip
4. Proper securement

1. Appropriate choice of the vein

- Easier and Safest Vein to be punctured
- For PICCs: avoid broken or paralyzed limbs
- Avoid to puncture already thrombosed vein
- Exit site
- Catheter - vein ratio

Maybe the most important factor: catheter to vein ratio



CHEST

Original Research

CRITICAL CARE

**The Effect of Catheter to Vein Ratio
on Blood Flow Rates in a Simulated
Model of Peripherally Inserted Central
Venous Catheters**

Thomas P. Nifong, MD; and Timothy J. McDevitt, PhD

Match the VAD caliber with the vein caliber:

- Inner vein diameter should be at least three times the catheter diameter
- 3Fr PICC = vein of 3 mm or larger
- 4 Fr PICC = vein of 4 mm or larger
- 5 Fr PICC = vein of 5 mm or larger
- 6 Fr PICC = vein of 6 mm or larger

Particularly for PICCs, dimensions do matter

Mermis 2014 (non-oncological pts)

5-6 Fr PICCs 7.6 %

4 Fr PICCs 0 %

McAuliffe 2016 (leukemia)

5-6 Fr PICCs 14.5 %

Koo 2017 (retrospective, 3020 PICCs)

proven relationship between CRT (4 %) and cath. size

Menendez 2016 (265 PICCs in children)

proven relationship between CRT (2.6 %) and cath. /vein ratio

Q3

**Is there any device or material which may
intrinsically reduce the risk?**

- **A lower diameter of the catheter might be protective against the risk of central venous thrombosis.**

Strength B Recommendation

2 – Appropriate technique of venipuncture

US guided venipuncture

Catheter-Related Central Venous Thrombosis: The Development of a Nationwide Consensus Paper in Italy

*Costantino Campisi, MD, Roberto Biffi, MD, and Mauro Pittiruti, MD
on behalf of the GAVeCeLT Committee for the Consensus*

Use ultrasound !

Prospective studies suggest a relationship between minimal insertion damage to vein wall and low rate of thrombosis.

Strength C Recommendation

Massimo Lamperti
Andrew R. Bodenham
Mauro Pittiruti
Michael Blaivas
John G. Augoustides
Mahmoud Elbarbary
Thierry Pirotte
Dimitrios Karakitsos

International evidence-based recommendations on ultrasound-guided vascular access

Use ultrasound !

Table 6 Recommendations regarding sterility using ultrasound guidance and prevention of infectious and mechanical complications using ultrasound-guided cannulation

Sterility during ultrasound vascular procedures

Domain code	Suggested definition	Level of evidence	Degree of consensus	Strength of recommendation
D8.S1	Sterile technique for catheter placement, including hand washing, gowns, and nose clips, using sterile ultrasound guidance	A	Very good	Strong
D8.S2	Prevention of infectious and mechanical complications using ultrasound guidance	A	Very good	Strong
D8.S3–4	A multi-faceted approach including ultrasound guidance, measures and the promotion of good practices applied by both medical and nursing staff, is suggested in order to reduce the incidence of CRBSI	A	Good	Strong
D8.S5	Ultrasound guidance should be used to avoid cannulation of thrombotic sites	A	Very good	Strong
D8.S6	Ultrasound guidance, by reducing puncture attempts, technical failure rates and mechanical complications, has to be preferred because of a reduced incidence of catheter-related thrombosis	A	Very good	Strong

Ultrasound guidance, by reducing puncture attempts, technical failure rates and mechanical complications, has to be preferred because of a reduced incidence of catheter-related thrombosis

Use ultrasound !

“... adoption of ultrasound guidance may have a significant favourable impact on the risk of catheter contamination and catheter related infection and on the risk of catheter related venous thrombosis”

(from SOR guidelines, 2008)

2 – Appropriate technique of venipuncture Use microintroducers !



Minimize vessel trauma



3. Adequate position of the tip

All the new guidelines agree that an incorrect tip position is a risk factor for "central" CRT

January 2008

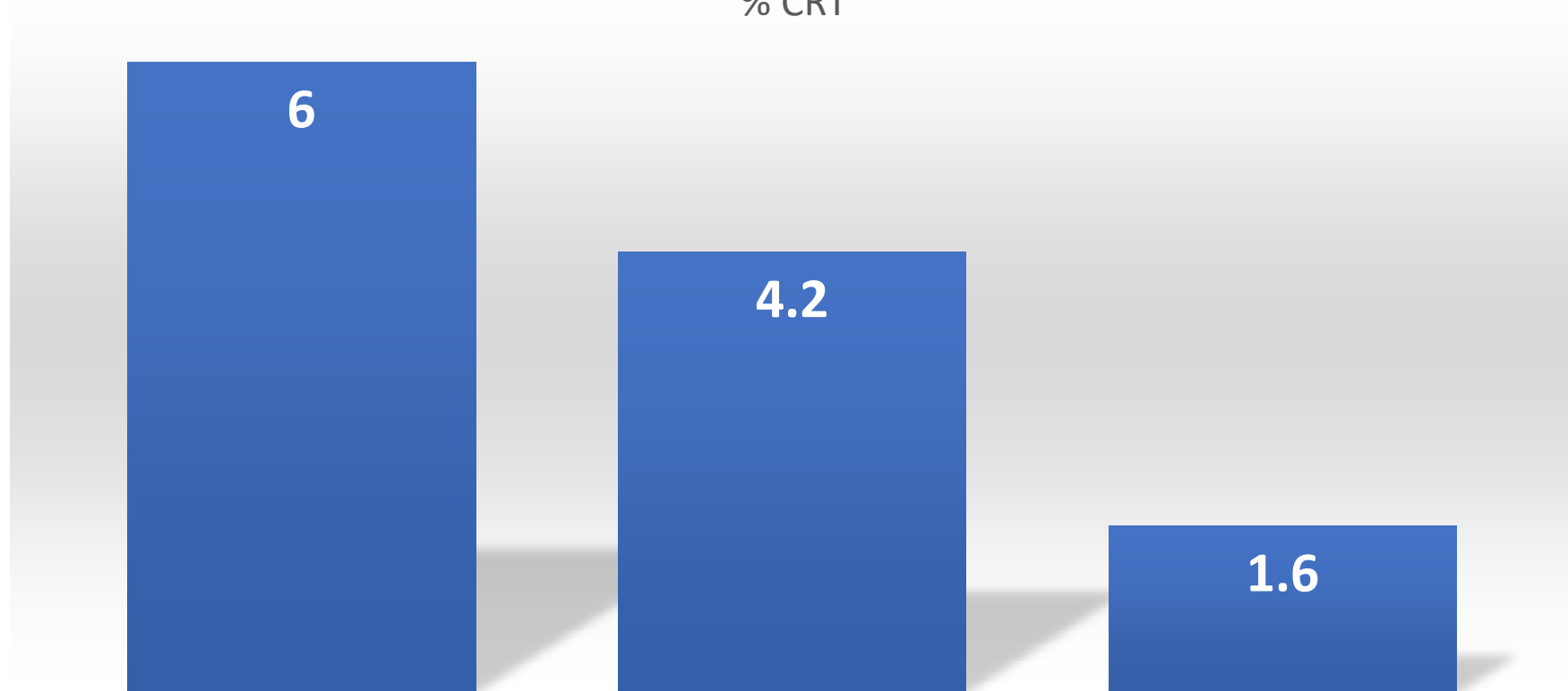
October 2008

August 2010

Tip location

Vein/Catheter ratio

% CRT



3. Adequate position of the tip

- **IC-ECG** is the method of choice for checking the position of the tip;
- It is an **economic, effective, simple** and **safe** methodology for a real-time assessment of the position of the tip of the catheter during the procedure itself;
- The **intra-procedural assessment** of the tip position avoids the costs and risks associated with repositioning the PICC

4 – Stabilize the catheter

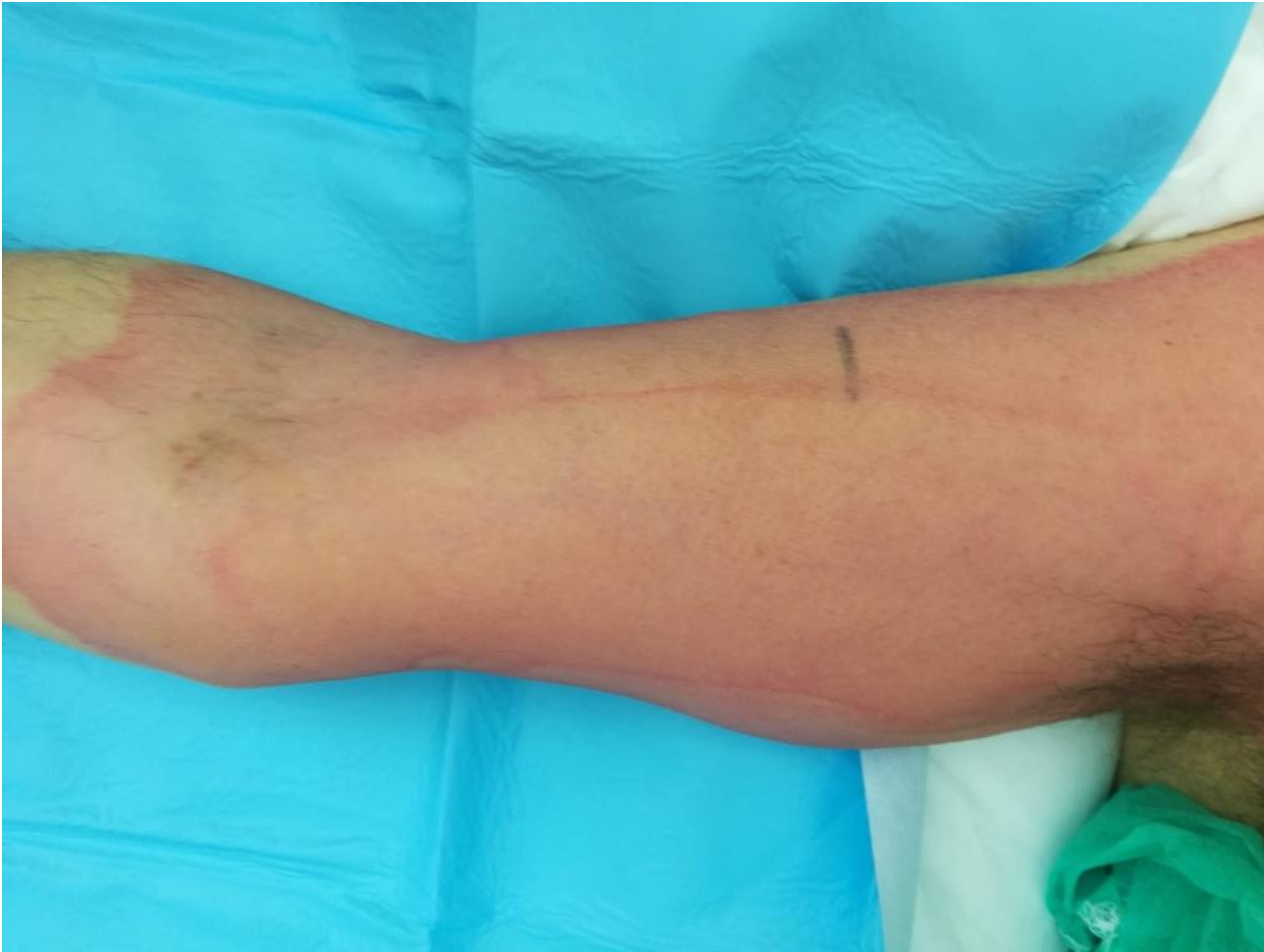
A 'mobile' VAD is more prone to exert mechanical trauma on the vein wall at the puncture site.

4 – Stabilize the catheter

Multimodal strategy

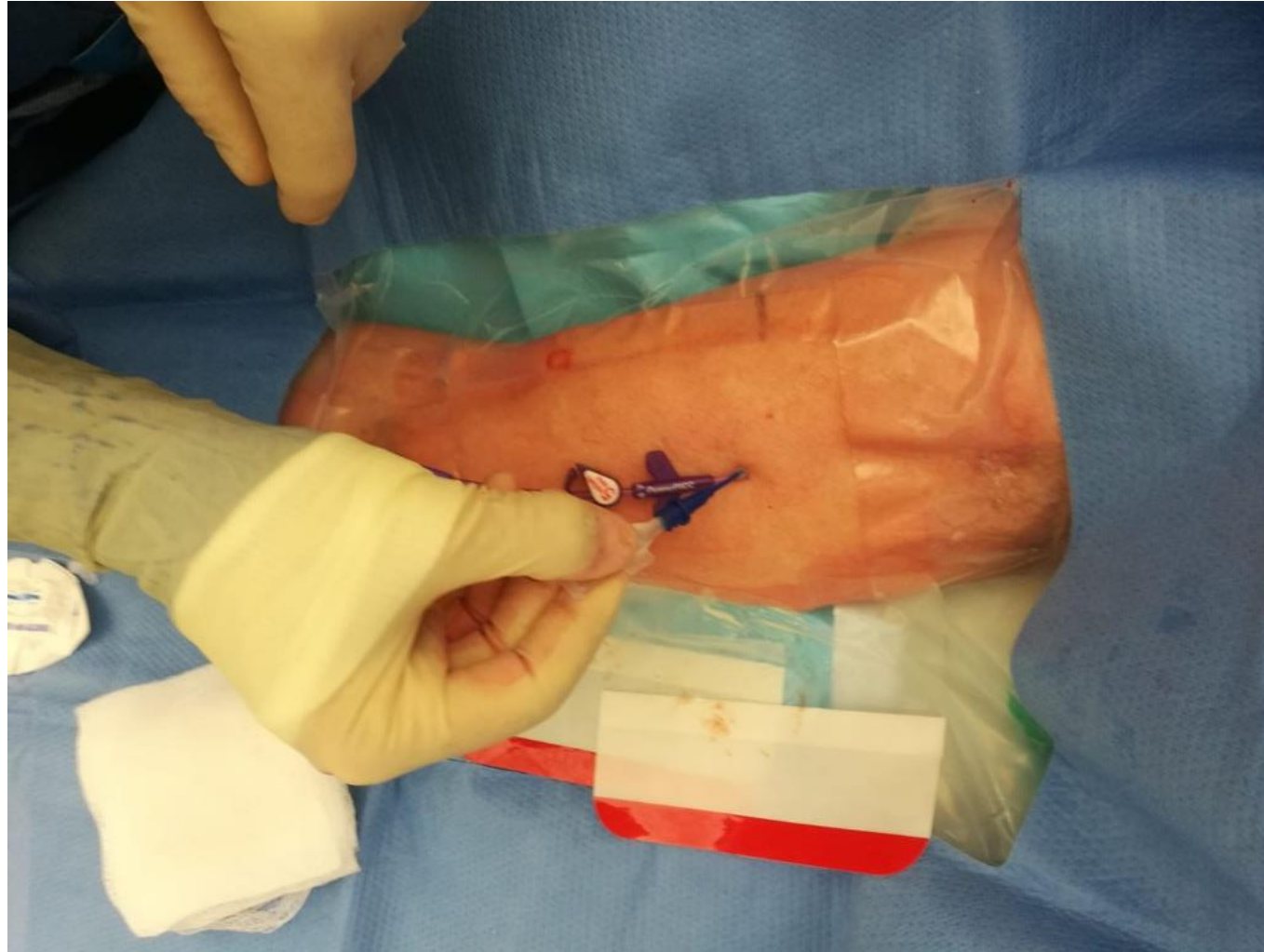
1. Proper choice of the exit site (mid-arm, infra-clavicular)
2. Cyanoacrylate glue at the exit site
3. Sutureless device (SAS to be preferred in patients at high risk of catheter displacement)
4. Exit site protection with semipermeable transparent membrane

4 – Stabilize the catheter

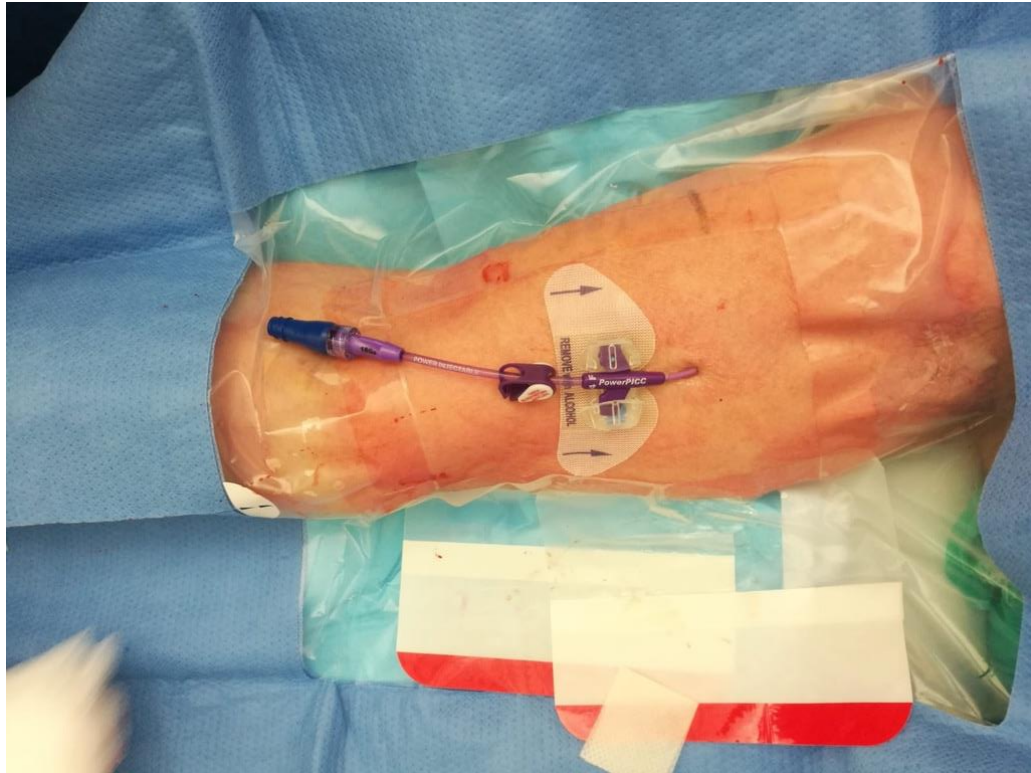


Mid-arm = excellent exit site

4 – Stabilize the catheter



4 – Stabilize the catheter



4 – Stabilize the catheter



TAKE HOME MESSAGES (1)

- CRT is a pathophysiological phenomenon, quite inevitable during any venous access procedure
- The magnitude (and clinical relevance) of CRT is related to factors that are largely out of our control
- We can control only few factors, mainly related to the **technique of insertion**

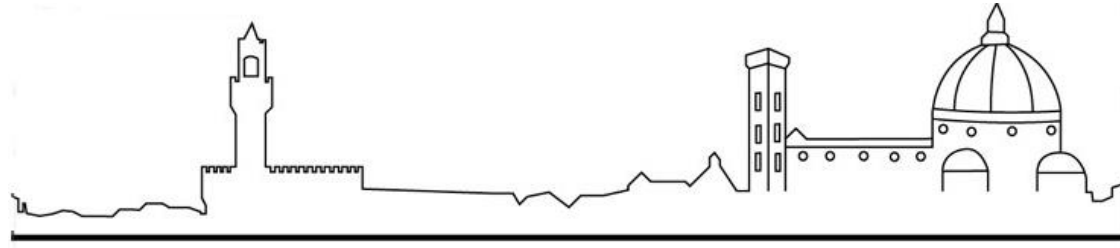
TAKE HOME MESSAGES (2)

- CRT may occur after PICC, or CICC, or FICC insertion
- The risk of thrombosis is certainly higher with FICCs
- There is no convincing data comparing PICC vs. CICC in terms of risk of thrombosis
- Though, in terms of morbidity and mortality, **PICC-related thrombosis is far less dangerous than CICC-related or FICC-related thrombosis**

TAKE HOME MESSAGES (3)

Use a **bundle** for CRT prevention:

- 1) Cath/vein size according to the 33% rule
- 2) Ultrasound venipuncture and micro-introducer kits
- 3) Tip location with intraprocedural, accurate methods (IC-ECG or echocardiography)
- 4) Proper stabilization of the catheter



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Thank you

Fulvio Pinelli, MD
Careggi University Hospital
Florence, Italy