# Trombosi venose dell'arto superiore

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# Outline

- Epidemiology
- Diagnosis of UEDVT
- Prevention of (catheter-related) UEDVT
- Treatment of UEDVT

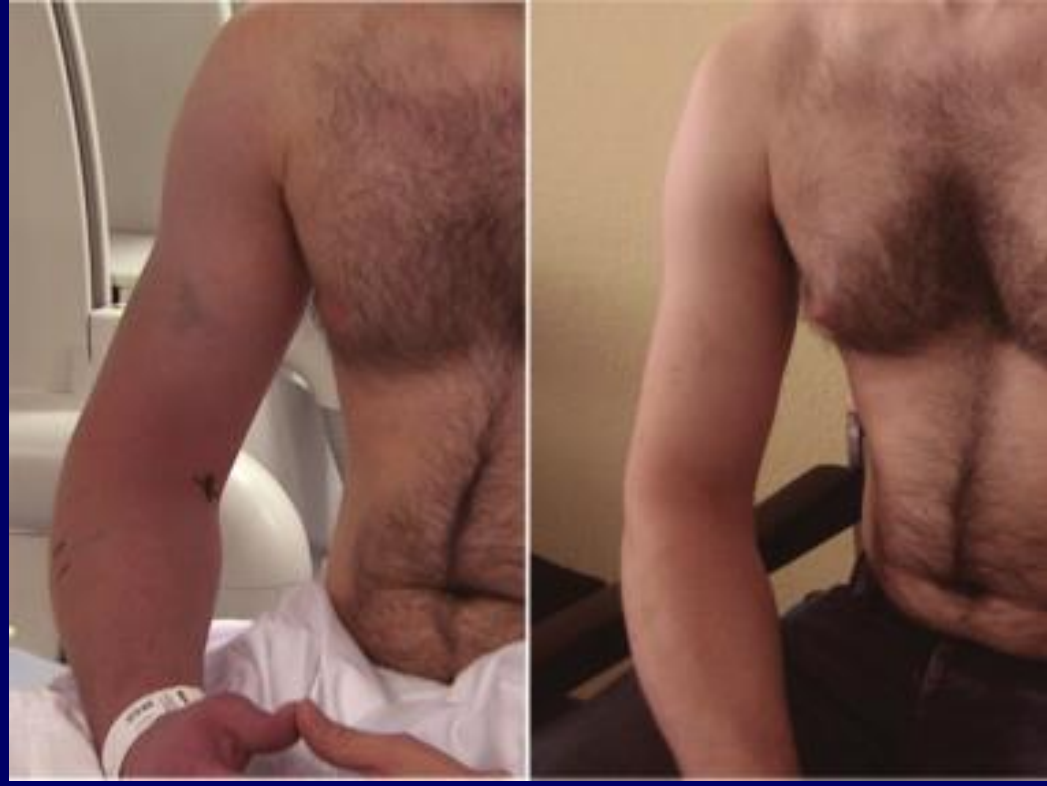
Lack of standardization as to which veins constitute the arm deep venous system

Mustafa Arch Intern Med 2002

- UESVT:cephalic, basilic, median antebrachial, median antecubital and accessory cephalic veins
- UEDVT: radial, ulnar, brachial, axillary, subclavian, internal jugular veins, brachiocephalic vein, and superior vena cava
  - Proximal UEDVT axillary or more proximal
  - Distal UEDVT brachial or more distal
- Axillary and subclavian veins most frequently affected

**Clinical Manifestations**

Heaviness
Discomfort
Pain
Paresthesia
Swelling of the affected arm
Symptoms of PE (e.g. dyspnea, visceral or pleuritic chest pain, hemoptysis)



*Physical examination*
Pitting edema
Redness
Cyanosis of involved extremity
Collateral veins shoulder/upper arm
Fever

CVC-associated UEDVT: failure to obtain blood return or difficulty infusing through a lumen.

# Etiology of UEDVT

## Primary UEDVT (25%)

- Effort-related thrombosis (Paget-Schroetter syndrome) often with underlying venous thoracic outlet Syndrome
- Venous thoracic outlet Syndrome
- Idiopathic

## Secondary (75%)

- Catheter-associated
- Pacemaker or defibrillator leads
- Cancer (ovary, lung cancer and lymphoma) with or without catheter
- Surgery
- Trauma
- Immobilization of the arm
- Pregnancy
- Oral contraceptive use
- Ovarian hyperstimulation syndrome

# Epidemiology

- Approximately 5-10% of cases of DVT
- Age-adjusted incidence 12-19 per 100,000 patients-yr

**Spencer et al. Am J Med 2007**

- 10-25% complicated by PE (5% symptomatic)
- 8% recurrent UEDVT

**Monreal M, et al.** Exp Oncol. 2006
**Prandoni P, et al.** BMJ 2004
**Flinterman LE, et al.** J Thromb Haemost. 2008
Kearon Chest 2012

**Table 3**
Incidence of recurrence, stratified by follow-up duration and subgroups.

| | Follow-up duration | | | |
|---|---|---|---|---|
| Recurrence rate | ≤ 3 months | 3 to12 months | >12 months | Combined* |
| All patients | | | | |
| Prospective studies | | | | |
| Events / total number of patients | 22/699 (3 studies) | 26/594 (2 studies) | 35/346 (4 studies) | 84/1661 (11 studies) |
| % (range) | 3.1 (0-4.1) | 4.4 (0-4.7) | 10.1 (0-13.4) | 5.1 (0-13.4) |
| Retrospective studies | | | | |
| Events / total number of patients | - | 23/241 (5 studies) | 58/766 (12 studies) | 126/1281 (20 studies) |
| % (range) | | 9.5 (0-14.5) | 7.6 (0-23) | 9.8 (0-26.1) |
| Subgroups | | | | |
| Cancer | | | | |
| Events / total number of patients | 12/301 (3 studies) | 2/24 (1 study) | 10/148 (3 studies) | 24/473 (7 studies) |
| % (range) | 4.0 (0-6.1%) | 9.2 | 6.8 (0-10) | 5.1 (0-10) |
| Central venous catheter (CVC) | | | | |
| Events / total number of patients | 10/228 (1 study) | - | 26/558 (1 study) | 36/782 (2 studies) |
| % (range) | 4.4 | | 4.7 | 4.6 (4.5-4.7) |
| Cancer + CVC | | | | |
| Events / total number of patients | 8/178 (2 studies) | - | 7/118 (2 studies) | 15 / 296 (4 studies) |
| % (range) | 4.5 (0-7.7) | | 5.9 (0-7.1) | 5.1% (0 – 7.7) |

*Follow-up ranged from 3 months to 5 years

Site of recurrent VTE (18 studies):

UEDVT 54% (ipsilateral in 76%, contralateral in 11%, 14% NR)
PE 21%
DVT legs 7%

Bleker Th Res 2016 in press

**Table. Incidence and Complications of Thrombosis of the Upper and Lower Extremities**

| | Upper-Extremity Thrombosis | Lower-Extremity Thrombosis |
|---|---|---|
| Annual incidence, n | 16/100 000 | 94/100 000 |
| Symptomatic pulmonary embolism, % | 2–9 | 15–29 |
| Recurrence at 12 mo, % | 2–4 | 6 |
| Postthrombotic syndrome, % | 7–47 | 20–50 |
| Overall 3-mo mortality, % | 11 | 7 |

Engelberg Circulation 2012

# Diagnosis of UEDVT

# Prevalence in suspected UEDVT

| | Costans | | | ARMOUR | Sartori | |
|---|---|---|---|---|---|---|
| | Cohort 1 | Cohort 2 | Cohort 3 | | Cohort 1 | Cohort 2 |
| N. patients | 140 | 103 | 214 | 406 | 239 | 483 |
| N. UEDVT | 50 (36%) | 46 (45%) | 65 (30%) | 103 (25%) | 24 (10%) | 64 (13%) |

Costans TH 2008
Kleinjan Ann Intern Med 2014
Sartori JAMA Intern Med 2015

# Clinical prediction rule: Constans rule

| | Regression coefficient | Odds ratio [95% CI] | P |
|---|---|---|---|
| Venous material* | 1.589 | 4.9 [1.9–12.5] | 0.0009 |
| Localized pain | 0.993 | 2.7 [1.2–6.3] | 0.017 |
| Unilateral pitting edema | 2.163 | 8.7 [3.4–22.2] | <0.0001 |
| Other diagnosis at least as plausible | –1.204 | 0.3 [0.1–0.8] | 0.016 |

* venous material including catheter or access device in a subclavian or jugular vein or pacemaker.

| Score | Derivation sample (N= 140) | Internal validation (N=103) | External validation (N=214) |
|---|---|---|---|
| | % [95% CI] (number with thrombosis /number in level) | | |
| ≤0 | 12% [10–23] (4/34) | 9% [0–20] (2/23) | 13 % [6–19] (14/110) |
| 1 | 20% [9–30] (11/56) | 37% [19–55] (10/27) | 38% [27–50] (26/68) |
| ≥2 | 70% [57–83] (35/50) | 64% [51–77] (34/53) | 69% [54–85] (25/36) |

Constans TH 2008

# D-dimer test

- Prospective study (n=52)
- Rapid quantitative ELISA
- Sensitivity100% (95% CI, 78–100%)
- Specificity 14% (95% CI, 4–29%)

Merminod et al . Blood Coagul Fibrinol 2006

- Prospective study (n=239)
- STA Liatest® D-Di microlatex
- Prevalence DVT 10%,  SVT 14.6%

| | DVT | SVT |
|---|---|---|
| Sensitivity | 92% (95%CI: 73-99%) | 77% (95%CI: 59-89%) |
| Specificity | 60% (95%CI: 52-67%) | 60% (95%CI: 52-67%) |
| NPV | 98% (95%CI: 93-100%), | 93% (95%CI: 86-97%) |

Sartori et al Th Res 2015

# Ultrasonography

| Type of US | Sensitivity | Specificity |
|---|---|---|
| CUS | 97 (90-100) | 96 (87-100) |
| Doppler | 84(72-97) | 94 (86-100) |
| CUS+Doppler | 91 (85-97) | 93 (80-100) |

Small studies, major methodological limitations
Two studies (157 patients) at low risk of bias evaluated the same US method and reached opposite conclusions

Di Nisio JTH 2010

# MRI

- One prospective study
- 44 consecutive patients, about half lost and not available for analysis.
- Time-of-flight

  Sens: 71% (95% CI, 29–96%)

  Spec: 89% (95% CI,52–100%)
- Gadolinium-enhanced

  Sens: 50% (95%CI, 12–88%)

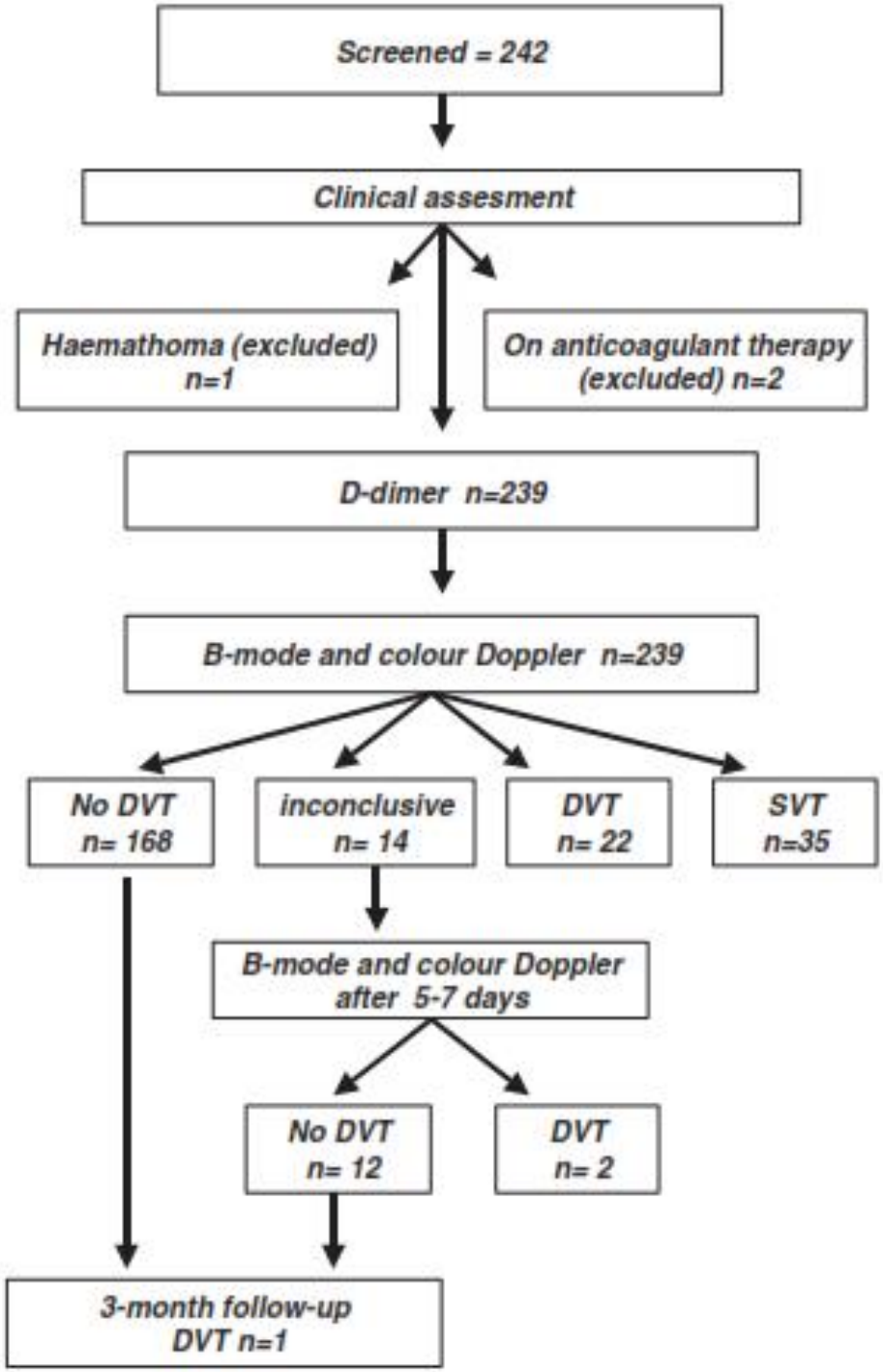
  Spec: 80% (95% CI, 44–97%)

Baarslag Acta Radiol 2004

# Diagnosis of UEDVT

- Paucity of studies and total of 793 pts
- Methodological limitations and small size
- No combination of tests within a diagnostic strategy

Di Nisio JTH 2010




## Failure rate

Single US: 1.3%, 95% CI: 0.46-3.61%
(3 DVT missed )

Serial US: 0.42%; 95% CI: 0.02-2.30%
(one DVT missed)

## Conclusions

Single US inconclusive in about 6% and UEDVT prevalence at second US not low (16.7%), suggesting that a single examination may not be sufficient to exclude UEDVT

Sartori Th Res 2013

# Diagnostic algorithm for UEDVT

- Sequential application of a clinical decision score, D-dimer testing, and ultrasonography

- Algorithm was feasible and completed in 390 of the 406 patients (96%)

- Prevalence:

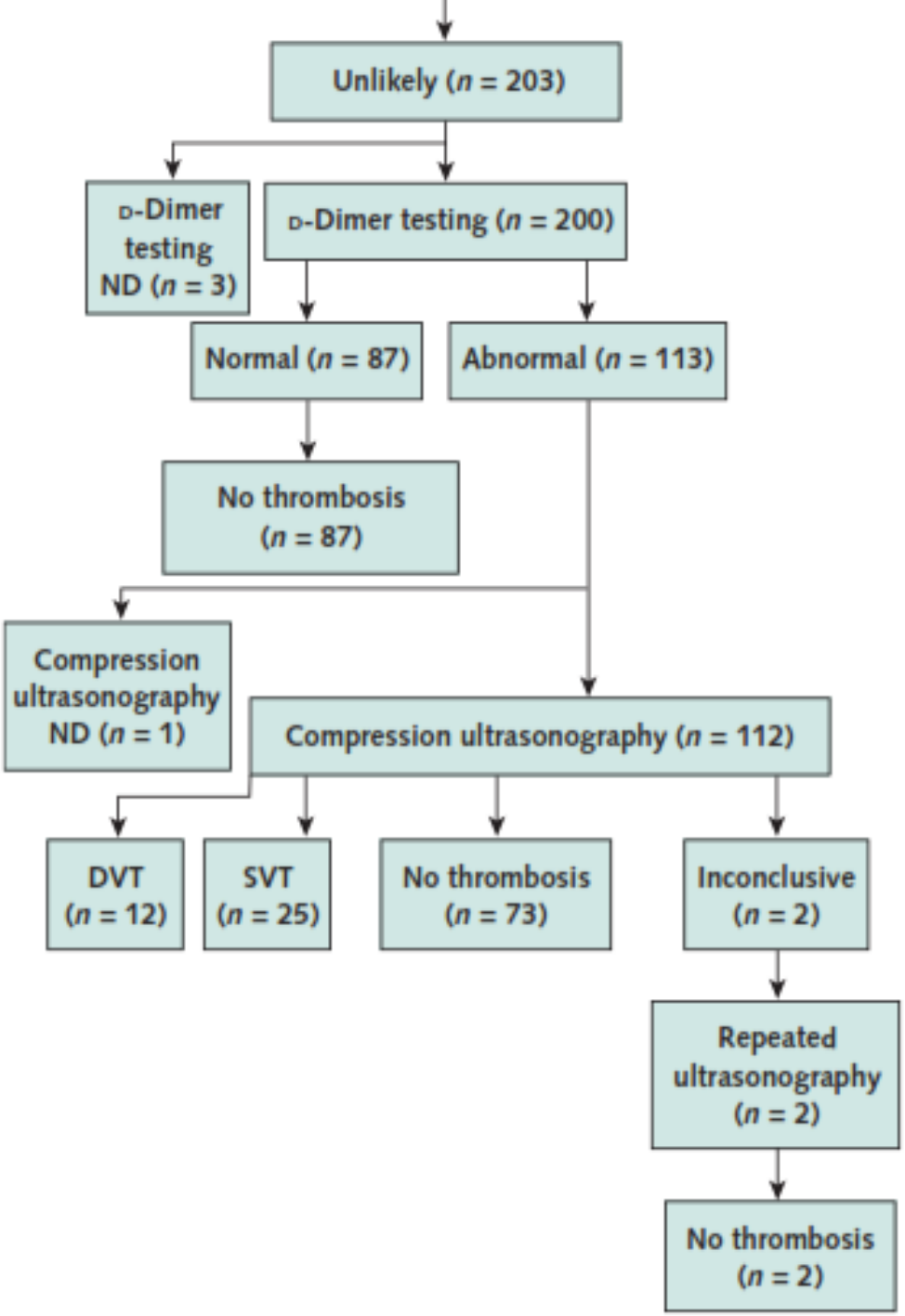
  Superficial venous thrombosis:  54 (13%)

  UEDVT : 103 (25%)

**Kleinjan Ann Intern Med 2014**

# Clinical prediction score: Constans

| Items | Points |
|---|---|
| CVC or pacemaker | 1 |
| Localized pain | 1 |
| Unilateral pitting edema | 1 |
| Plausibility of another diagnosis | -1 |
| ≤1<br>≥2 | Unlikely<br>Likely |
| Sensitivity<br>Specificity | 78% (95% CI, 68–88%)<br>64% (95% CI, 57–72%) |

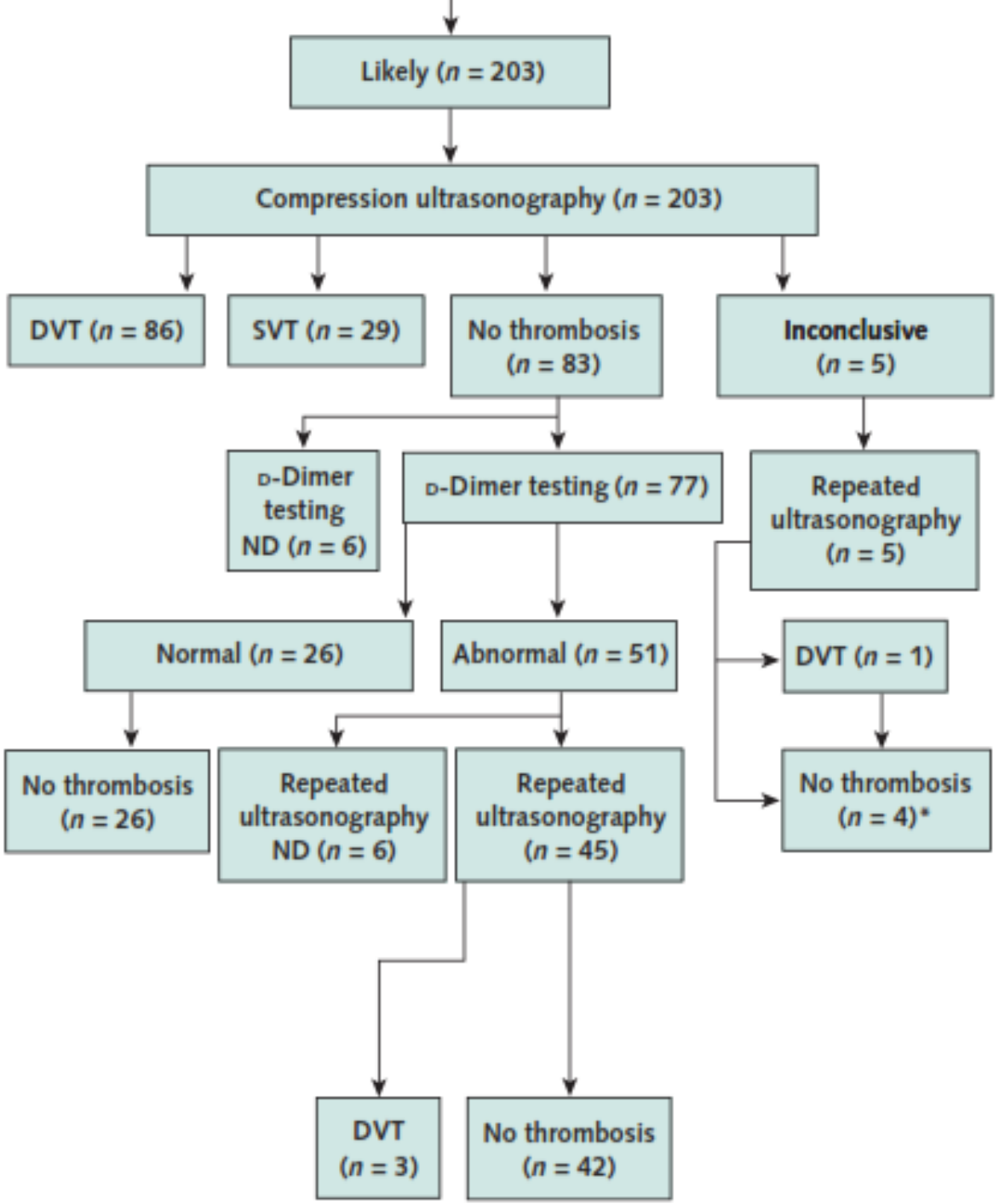



➢**DDimer NORMAL**

21% (95% CI, 17% to 25%) UEDVT safely excluded without US

No VTE at 3-mo fup
Failure rate, 0.0% [CI, 0.0% to 4.2%]).

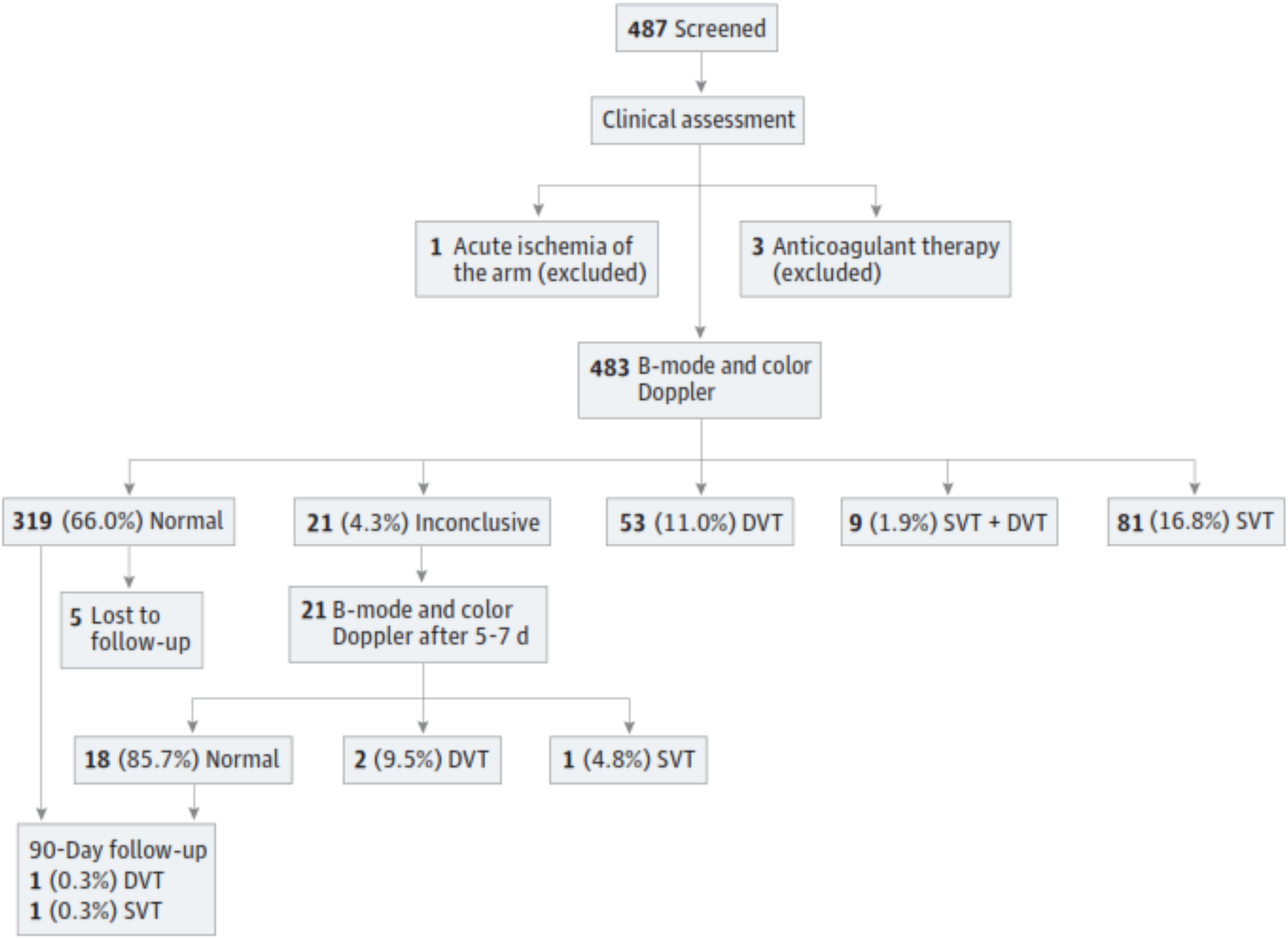
➢**Ddimer ABNORMAL**
Failure rate 0.0% (0 of 75 [CI, 0.0% to 4.8%])




**Overall failure rate**
**0.4% (95% CI, 0.0% to 2.2%)**

Indeterminate US (1.7%)

Serial US in 51 patients (13%): 3 UEDVTs


487 Screened
Clinical assessment
1 Acute ischemia of the arm (excluded)
3 Anticoagulant therapy (excluded)
483 B-mode and color Doppler
319 (66.0%) Normal
21 (4.3%) Inconclusive
53 (11.0%) DVT
9 (1.9%) SVT + DVT
81 (16.8%) SVT
5 Lost to follow-up
21 B-mode and color Doppler after 5-7 d
18 (85.7%) Normal
2 (9.5%) DVT
1 (4.8%) SVT
90-Day follow-up
1 (0.3%) DVT
1 (0.3%) SVT

# Armour study vs. Sartori study

| Characteristic, % | ARMOUR | Sartori |
|---|---|---|
| Prevalence UEDVT | 25 | 13 |
| Cancer | 34 | 17 |
| CVC | 35 | 7 |
| Inpatients | 20 | 0 |

In the ARMOUR US was safely witheld in 21%

# Prevention of catheter-related UEDVT

**Definition of Catheter-related UEDVT:**

**Venous thrombosis involving the vein(s) in which the catheter dwells.**

Other common, but usually less problematic, thrombotic complications:

- Fibrin sheath along the length of the catheter
- Ball-valve-type clot on the tip of the catheter
- Catheter lumen obstruction
- Superficial thrombophlebitis of the cannulated peripheral vein

Usually nuisance-type problems: localized symptoms or interfere with infusion into or aspiration from the catheter, but do not cause systemic complications.

Lee JTH 2012

# Prevention of catheter-related UEDVT

>5 million central venous access devices or catheters inserted annually in USA

Catheter-related UEDVT represents 70–80% of all UEDVT and 10% of all cases of VTE

Incidence of CVC-associated UEDVT:

symptomatic 5%

asymptomatic 14–18%

Lee JTH 2012
Shivakumar JCO 2009

**Table 1** Potential risk factors for catheter-related thrombosis

| |
|---|
| Catheter-related |
| Catheter design (PICC > Hickman > implanted port) [16] |
| Material (polyethylene or polyvinylchloride > silicone or polyurethane) [56,57] |
| Presence of valves (nonvalved > valved) [58,59] |
| Catheter tip position (proximal to SVC and RA junction) [16,60–64] |
| Number of lumens (triple > double > single) [13,64] |
| Larger catheter caliber or diameter [65,66] |
| Catheter occlusion [14] |
| Insertion-related |
| Vein entry (femoral > subclavian > jugular) [67,68] [16,69] |
| Insertion technique (percutaneous > cut-down > ultrasound guided) [70] |
| Left-sided insertion (> right-sided) [61,63,71] |
| Previous catheterization, traumatic insertions or multiple attempts [14] |
| Patient-related |
| History of venous thromboembolism [13,16,72] |
| Heritable thrombophilia [21–23] |
| Infection [7,8,36] |
| Tumour type and status [14,63] |

Type of infusion:

Total parenteral nutrition increases tonicity of the infusate (?), not widely studied.

Sclerosing chemotherapeutic agents

Lee JTH 2012

Shivakumar JCO 2009

# Prevention of Catheter-related UEDVT

- Efficacy and safety of **heparin flushing or heparin-bonded catheters** questionable

- **Anticoagulant prophylaxis** to prevent CRT in cancer patients largely ineffective

  WARP (warfarin 1mg/d or INR 1.5-2.0) study vs. no prophylaxis: major bleeding 3.4% vs. 1.5%, p=0.09)

**Routine anticoagulant prophylaxis not recommended**

Studies underpowered, because of the unexpected low event rates in the control groups

# Treatment of UEDVT

# Clinical course of upper extremity deep vein thrombosis in patients with or without cancer: a systematic review

Systematic search of the literature (MEDLINE, EMBASE and BIOSIS Previews)

45 studies 4580 patients (12 to 598)

**No RCTs**

UEDVT associated with cancer in 44% (range 0 to 74%) and with CVC in 53% (range 0 to 93%)

Bleker Th Res 2016 in press

# Clinical course of upper extremity deep vein thrombosis in patients with or without cancer: a systematic review

**Treatment of UEDVT**

- **Thrombolysis** (8 studies; 230 patients)

- **Anticoagulant therapy (27; 3271 patients)**

  *Initial treatment (i.e. in the first 5 to 10 days)*

  UFH 13%

  LMWH 86%

  *Long-term treatment (median duration of 3 to 6 months)*

  LMWH 32%

  VKAs 56%

  Cancer patients: some of the older studies, VKA prescribed to all.
  Muñoz et al 2008, 75% LMWH and 25% VKA

Bleker Th Res 2016 in press

## Conclusions

- Average incidence recurrent VTE 5.1%
- Average incidence bleeding 3.1%

} 3 – 59 months fup

- Major bleeding 7.9% - 17% in systemic (2 studies) and 9% in catheter directed (1 study) thrombolysis

- Cancer patients: three-fold higher risk of recurrent VTE and 4-fold risk of anticoagulant-related bleeding

Recurrence after 3 months, 7.7% cancer + CVC-related UEDVT vs. 4.4% cancer with non-CVC-related UEDVT

Bleker Th Res 2016 in press

# Current management strategies and long-term clinical outcomes of upper extremity venous thrombosis

102 UEDVT. Median FUP 3.5 years (IQR 2.9 to 4.0)

Anticoagulant treatment

100 patients (98%)

Median duration 182 days (IQR 91 to 365), 29% treated indefinitely

**Long-term treatment:** VKA 56% - LMWH 41%

Cancer: 78% LMWH monotherapy

Non cancer: 81% VKA

Elastic compression stockings for the arm: 30%

CVC removal: 6%

Bleker JTH 2016 in press

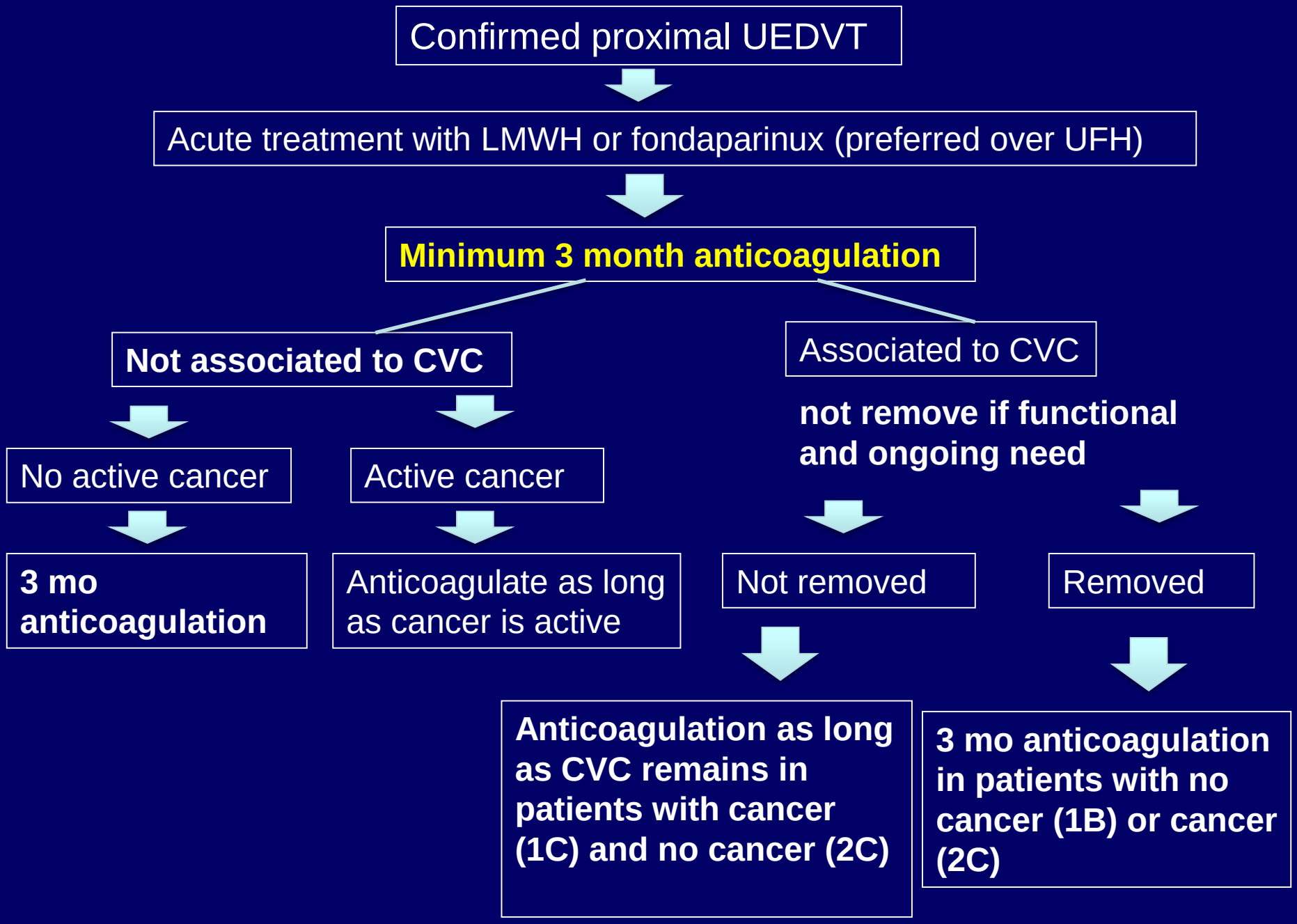
# Clinical outcomes in patients with and without cancer

Overall
9% recurrent VTE (5 on therapy, 2 LMWH and 3 on VKAs)
5% major bleeding
26% death
8% moderate post-thrombotic symptoms

Cancer patients

18% recurrent VTE versus 7.5% in non-cancer
(adjusted HR 2.2, 95%CI 0.6 to 8.2)

No MB in cancer patients




Kearon Chest 2012

## Treatment of distal UEDVT

- Clinical or ultrasound surveillance to detect extension of UEDVT while withholding anticoagulation
- Prophylactic or therapeutic dose anticoagulation for 3 months

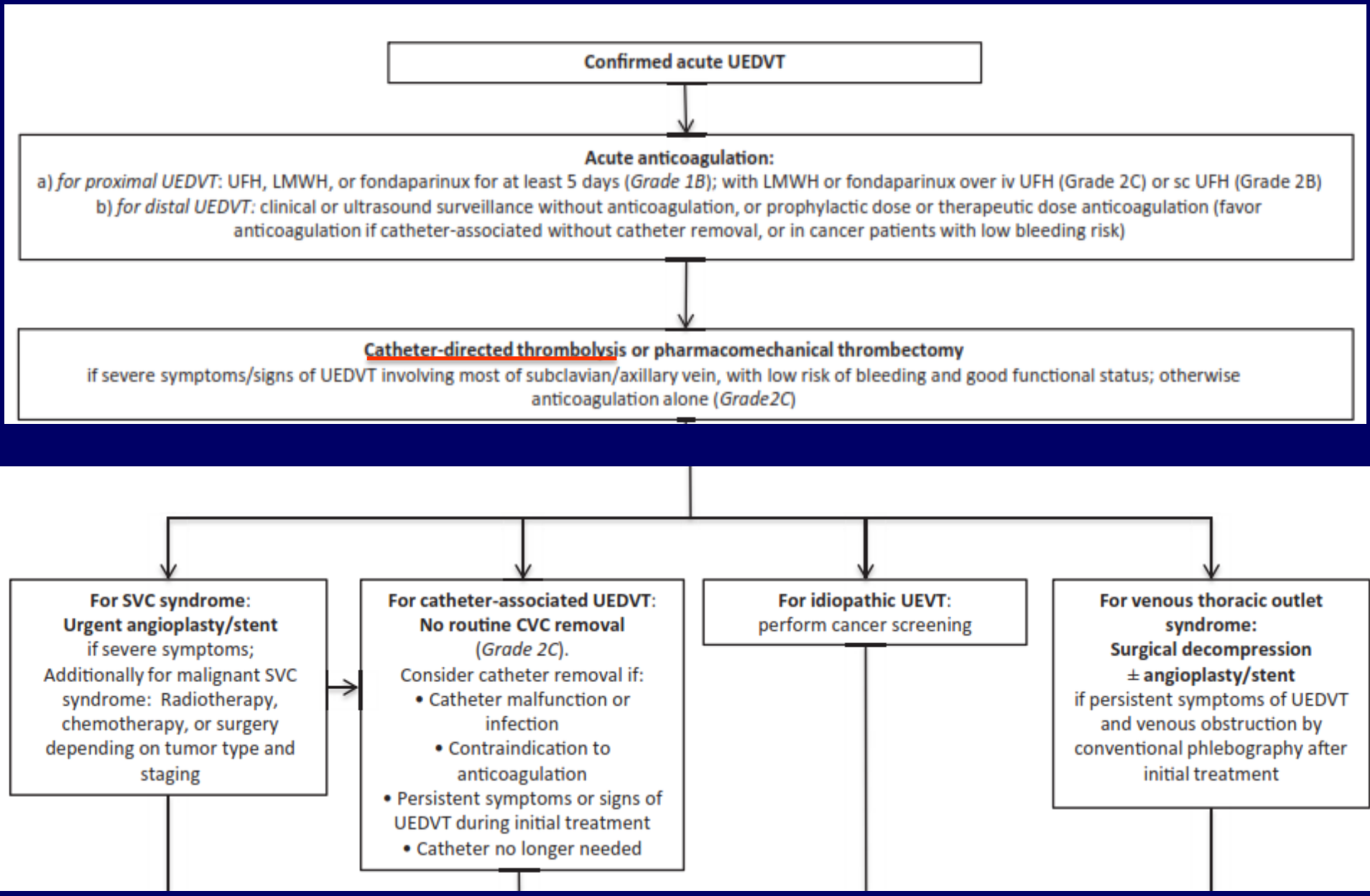
Favor anticoagulation if:
symptomatic
associated with CVC that will remain in place
associated with cancer in the absence of CVC

Kearon Chest 2016

## Compressions sleeves or bandages or venoactive drugs

Lack of studies
Not recommended
useful for the treatment of PTS?

Engelberg Circulation 2012
Kahn Circulation 2014




Engelberg Circulation 2012

# Removal of the CVC

- **Infection:** antibiotics and anticoagulation. Removal if bacteremia persists despite systemic antibiotic therapy

- **Loss of catheter function:**

Therapeutic anticoagulation

Instilling small doses of a thrombolytic agent into the catheter lumen

If not effective, reassess patency after few days of therapeutic LMWH

If the catheter remains obstructed, remove and replace

Lee JTH 2012

# Outcome of central venous catheter associated upper extremity deep vein thrombosis in cancer patients

Retrospective cohort of cancer outpatients (n= 99) with symptomatic CVC-associated proximal UEDVT

Median anticoagulation: 124 days (range 40 to 1849)

CVC pulled in all patients in remission and in 26/29 (89.6%) with active cancer

**Recurrent VTE**

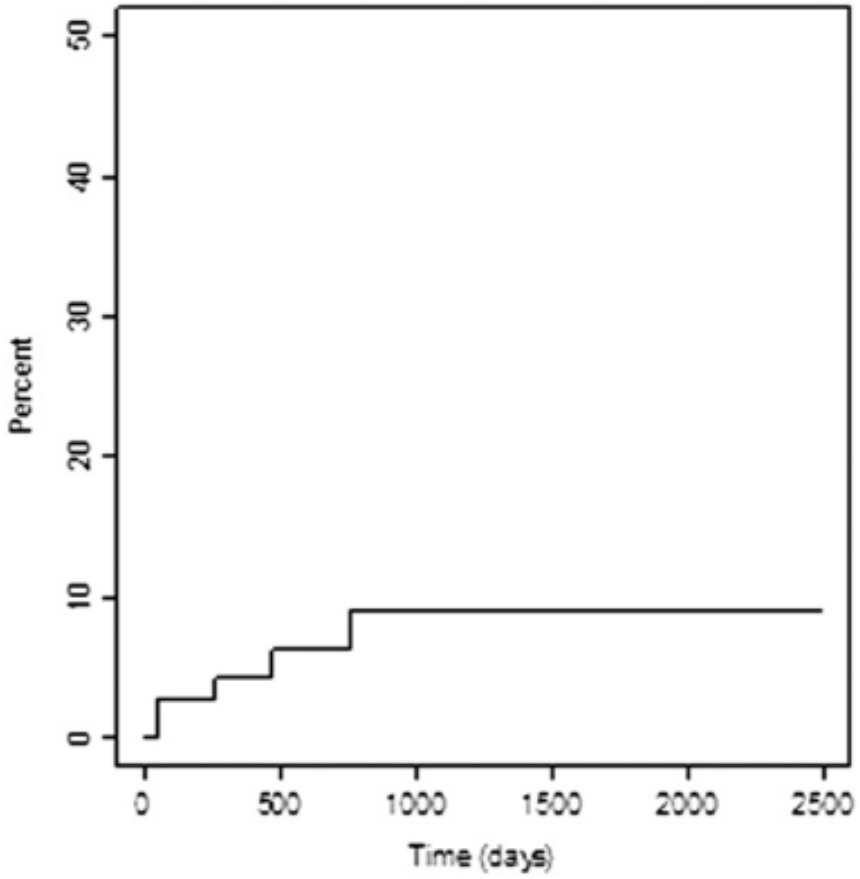
Frst 3 months of treatment: no recurrent VTE and 2 major bleeding

Follow-up: 5 recurrent VTE (3 PEs, 1 superior vena cava thrombosis after port-a-cath insertion, and 1 ipsilateral recurrent UEDVT)

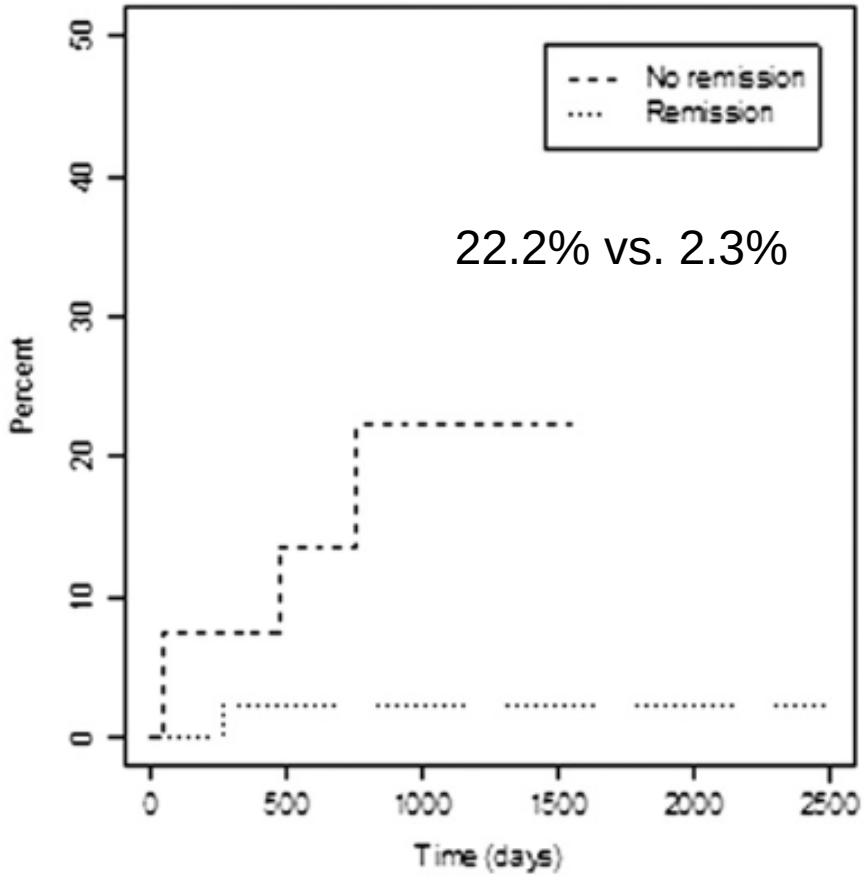
Delluc et al Th Res 2015

# Cumulative probability of recurrence

Overall




By cancer status at discontinuation




Delluc et al Th Res 2015

Grazie per l’attenzione

# Trombosi venose dell'arto superiore

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# Risk factors and clinical presentation

| | C | SVT | DVT | |
|---|---|---|---|---|
| | n = 179 | n = 35 | n = 25 | p-value |
| Age (years) ± SD: | 58.8 ± 16.9 | 51.8 ± 14.5 | 64.0 ± 16.8 | 0.014 |
| Male: | 33.5% | 48.6% | 42.3% | 0.221 |
| D-dimer (ng/mL) ± SD | 677 ± 797 | 1838 ± 2940 | 2917 ± 4872 | 0.001 |
| *Venous thromboembolism risk factors (%)* | | | | |
| Active cancer: | 18.3 | 14.7 | 7.7 | 0.411 |
| CVC: | 4.0 | 2.9 | 24 | 0.001 |
| PM: | 1.1 | 0 | 8.0 | 0.030 |
| History of vein thrombosis: | 10.6 | 8.6 | 12.0 | 0.904 |
| Oestrogen-containing therapy: | 2.5 | 3.0 | 7.7 | 0.348 |
| Peripheral vein infusion | 12.1 | 61.8 | 7.7 | 0.0001 |
| *Symptoms (%)* | | | | |
| Pain: | 72.5 | 93.8 | 79.2 | 0.033 |
| Oedema: | 58.2 | 31.3 | 84.0 | 0.001 |
| Redness or rash: | 18.8 | 62.5 | 32.0 | 0.001 |

Sartori et al . Th Res 2015

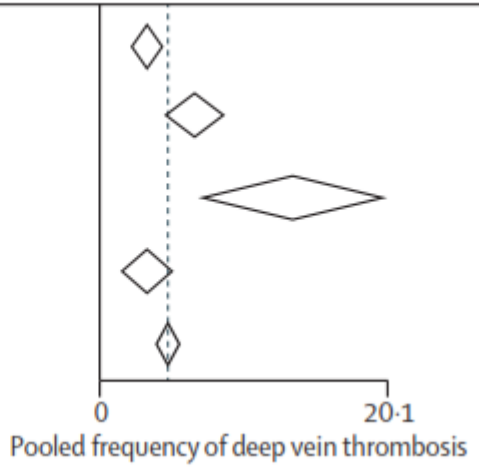
# Risk of VTE associated with peripherally inserted central catheters

**64 studies (n= 29 503)**

58% did not report on pharmacological VTE prophylaxis

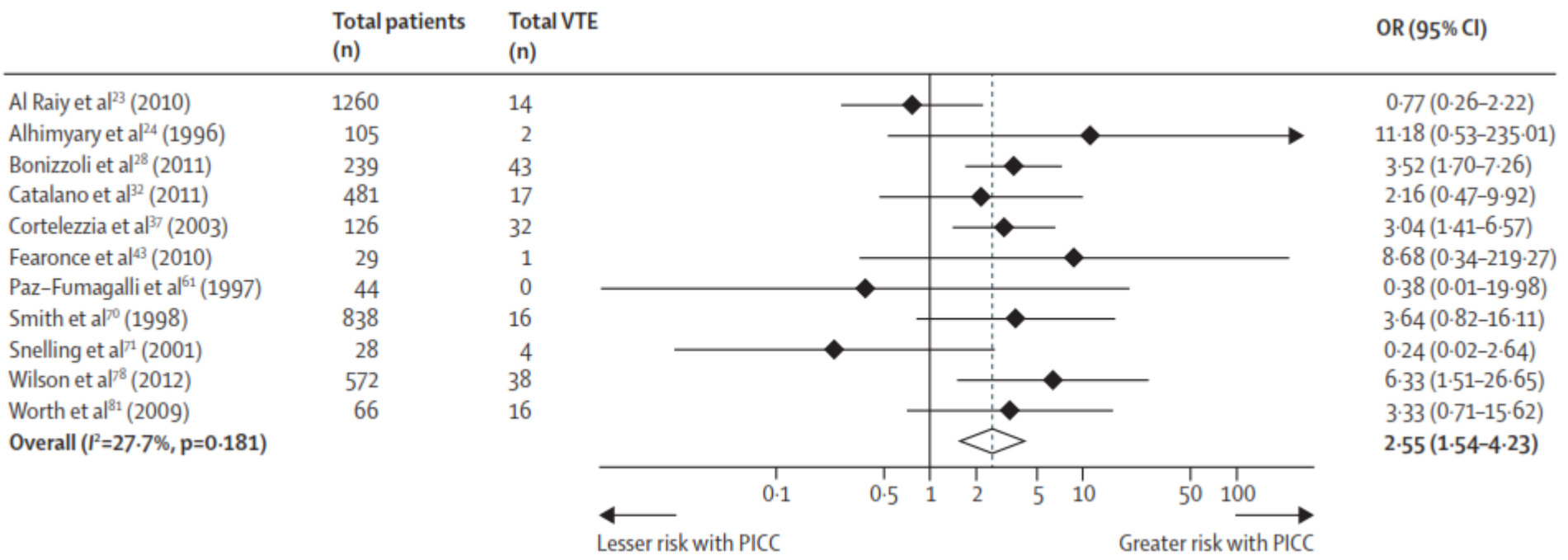
Time to UEDVT after PICC insertion: 8.7 days (range 3–22)

| | Total patients (n) | Total VTE (n) | % VTE (95% CI) |
|---|---|---|---|
| Patients admitted to hospital | 11476 | 349 | 3·44 (2·46–4·43) |
| Patients with cancer | 3430 | 234 | 6·67 (4·69–8·64) |
| ICU patients | 1219 | 128 | 13·91 (7·68–20·14) |
| Various patients | 9462 | 281 | 3·44 (1·70–5·19) |
| **Overall** | **25587** | **992** | **4·86 (4·08–5·64)** |




Chopra Lancet 2013

# PICC vs. CVC




Chopra Lancet 2013