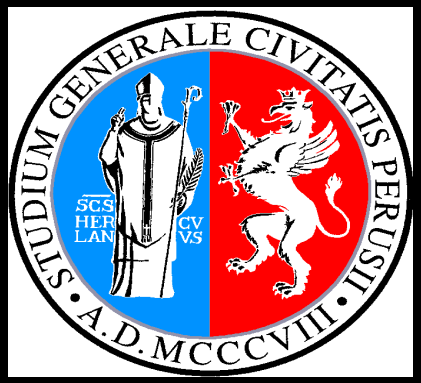
Central venous catheter-related thrombosis

Giancarlo Agnelli

Medicina Interna & Cardiovascolare - Stroke Unit

Scuola di Specializzazione in Medicina di Emergenza - Urgenza

Università di Perugia



My talk today

- Epidemiology
- Antithrombotic prophylaxis:
  - evidence from literature
  - interpretation of the available data
- Future perspectives

Background

The use of long-term CVC has considerably facilitated the administration of chemotherapy as well as supportive therapy in cancer patients

Determinants of CVC-related thrombosis

Vessel injury related to the CVC insertion procedure

Venous stasis caused by the indwelling CVC

Activation of blood coagulation associated with cancer

My talk today

- Epidemiology
- Antithrombotic prophylaxis:
  - evidence from literature
  - interpretation of the available data
- Future perspectives

What is the incidence of CVC-related thrombosis?

Inconsistencies in:

Study design & population

Catether insertion techinique

Definition of VTE events

Accuracy of diagnostic test

Risk factors of CVC-related thrombosis

Gender
Age
Body mass index — Patient related
Thrombophilia
Cancer site
Cancer histology — Cancer-related
Metastases
Chemotherapy

MISSING DATA

CVC-related
CVC type & diameter
CVC insertion
CVC tip position
CVC care (time interval)
CVC lumen

PUBLISHED DATA

Risk Factors for CVC-related DVT

Position of CVC tip

- CVC tip in proximal SVC are more thrombotic than those at the junction between SVC and right atrium

McGee, Cri Care Med 1993, Caers, Supp Care Cancer 2004
Puel, Cancer 1993, Cadman A Clin Rad 2004
Petersen J Am J Surg 1999, Tesselaar, Eur J Cancer 2004

Side of CVC insertion

- left CVC position are at higher risk of thrombosis tha right position of CVC

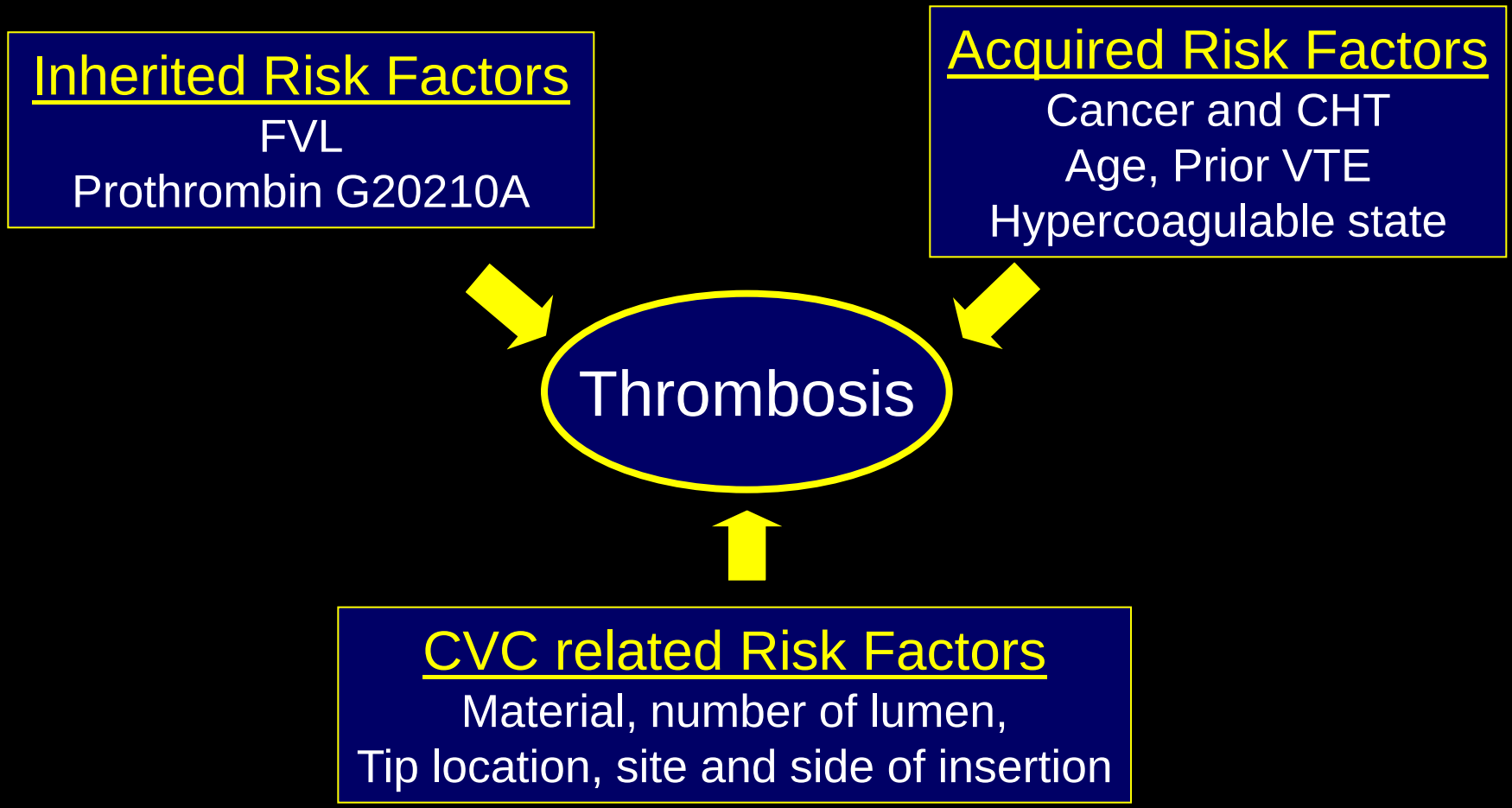
Puel, Cancer 1993, Craft, Aust NZJ Med, 1996
De Cicco, Thromb Res 1997, Unal AE, Trasf Apher Sci 2003
Tesselaar, Eur J Cancer 2004

N° of CVC lumen

- triple-lumen Hickman CVC have a higher risk than double lumen

Eastridge BJ, JCO 1995

Interaction of RF for CVC-related DVT



Type of thrombotic complications

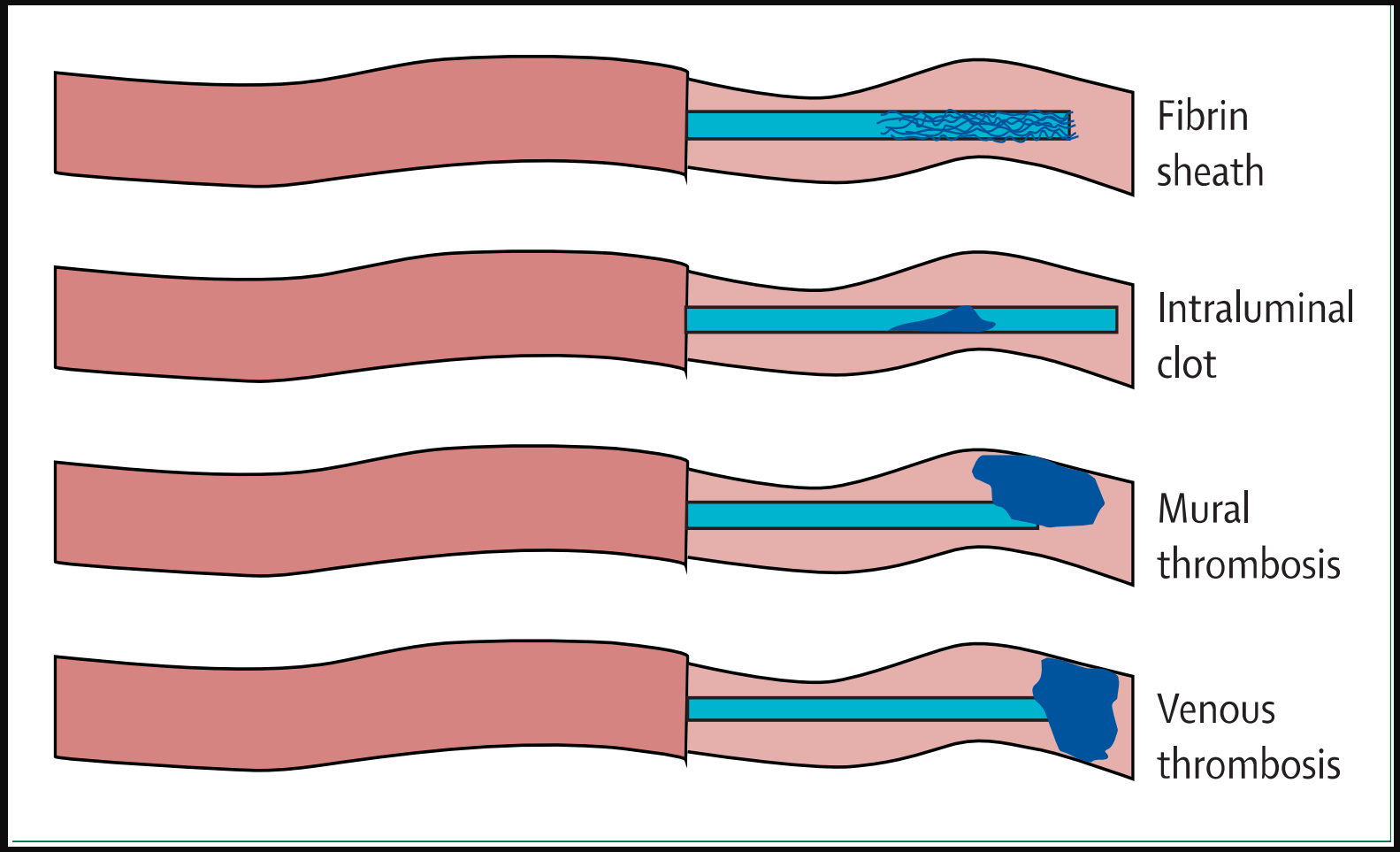
Limited to the catheter tip ⇨ Ball-valve effect

Around the CVC ⇨ Fibrin sheath

On the catheterized vein ⇨ Venous Thrombosis

(with or without extension to the proximal veins)

Type of thrombotic complications

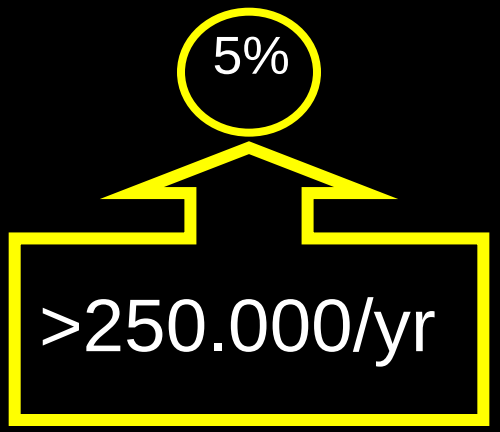


Baskin et al., Lancet 2009

Epidemiology

About 5.000.000 CVC/year

- 15% have complications (750.000 patients/year)
  - Mechanical (at the insertion of CVC) 5-19%
  - Infection 5-26%
  - Thrombotic 2-26%
    - Fibrin sheath < 40%
    - Mural thrombosis 5%



Modified by McGee, NEJM 2003

My talk today

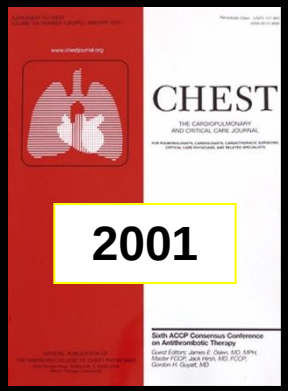
- Epidemiology
- Antithrombotic prophylaxis:
  - evidence from literature
  - interpretation of the available data
- Future perspectives

Antithrombotic prophylaxis

The initial studies

		treatment (% thrombosis)	controls
Bern, 1990	Warfarin 1mg	9.5	37.5
Monreal, 199	Dalteparin 2500IU	6	62

ACCP 2001 Guidelines



"Patients with long term central lines for chemotherapy should also receive prophylaxis with either warfarin 1 mg daily or subcutaneous LMWH to prevent axillary-subclavian vein thrombosis."

The impact of this recommendation on clinical practice has been largely unknown !

Use of thromboprophylaxis

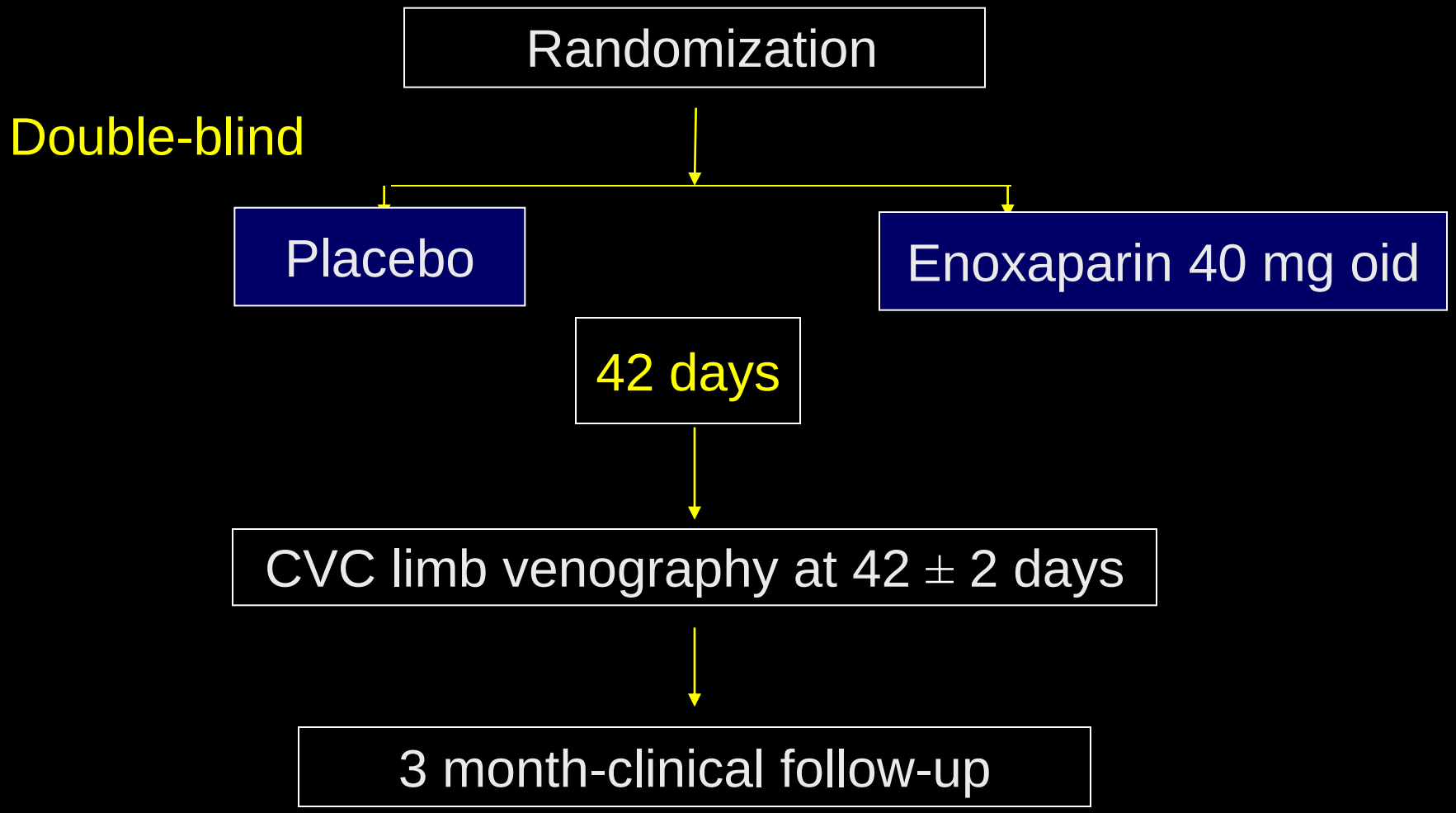
	% of responders	
Never	19	45%
Rarely	26	
Sometimes	22	
Usually	31	
No response	2	

FRONTLINE: Kakkar et al., the Oncologist 2003

Prophylaxis for CVC-related DVT: randomized trial

Author, year	Study design	n	Prophylactic regimens	Duration	Endpoint assessment	CVC-DVT %	P value
Bern, 1990	P, Open	82	Warfarin 1 mg no treatment	90 days	mandatory venography	9.5 37.5	<0.001
Monreal, 1996	P, Open	29	Dalteparin 2500 U no treatment	90 days	mandatory venography	6 62	0.002
Reitchard, 2002	R,DB	439	Dalteparin 5000 U Placebo	16 weeks	symptomatic events	3.7 3.4	0.90
Couban, 2003	R, DB	255	Warfarin 1 mg Placebo	variable	symptomatic events	4.6 4.0	0.81
Verso, 2004	R, DB	385	Enoxaparin 40 mg Placebo	42 days	mandatory venography	14.1 18.0	0.35

Ethic Study: Study Design



Verso et al., J Clin Oncol 2005

Ethics: sample size assumptions

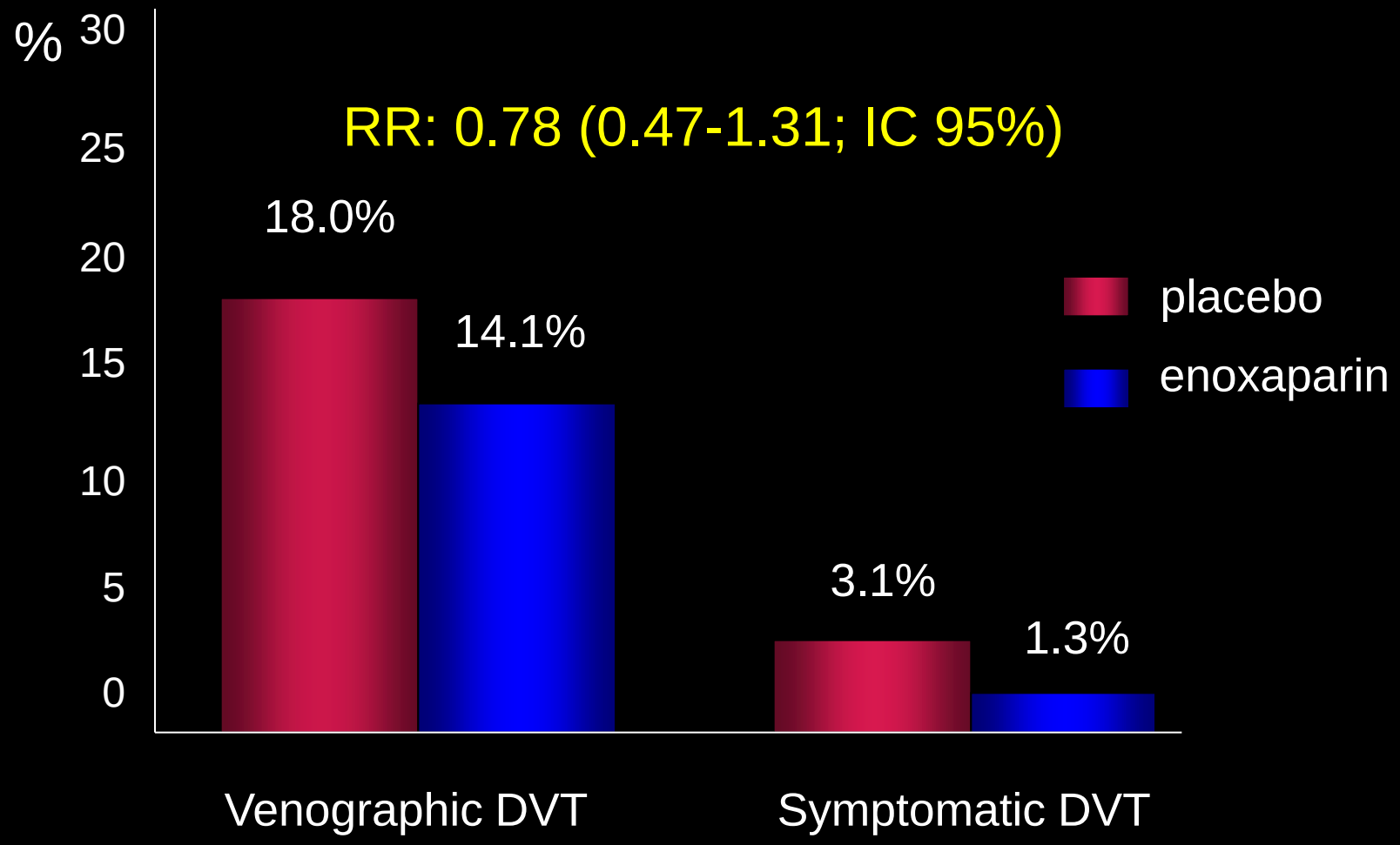
VTE in the placebo group $\geq$ 30%

VTE in the enoxaparin group $\leq$15%

α=0.05 (two side test), β= 0.80

Verso et al., J Clin Oncol 2005

ETHIC Study: Results



Verso et al., J Clin Oncol 2005

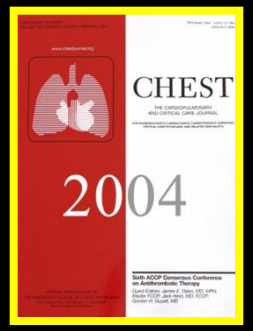
Incidence of Major Bleedings

Author, yrs	Population	Study Treatment	N	Major Bleeding (%)
Verso, 2005	Oncology	Enoxaparin 4000 IU/die	191	0
		Placebo	194	0
Karthaus, 2006	Oncology	Dalteparin 5.000IU/die	294	1 (0.3)
		Placebo	145	0
Couban, 2005	Oncology	Warf 1 mg/d	130	0
		Placebo	125	3 (2.4)
WARP, 2006	Oncology	Warfarin AD	473	9 (1.9)
		Warf 1mg/d	471	7 (1.5)
		Placebo	403	1 (0.2)

ETHICS: interpretation of the results

- Enoxaparin less effective than expected (increase dose!)
- Incidence of CVC-related DVT lower than expected (insufficient sample size?)
- Inconsistency of risk for CVC-related thrombosis across the study population (background noise!)

2004 Guidelines



"We suggest that clinicians not routinely use prophylaxis to try to prevent thrombosis related to long-term CVCs in cancer patients (grade 2B). Specifically, we suggest that not use LMWH (grade 2B) and we recommend against the use of fixed dose warfarin (grade 1B) for this indication."

"Prophylaxis with LMWH or 1 mg low dose of warfarin are not recommended (grade II B)."

12 studies (2 in children)

2823 patients (2664 adult patients)

Akl et al., The Cochrane Library 2014

THE COCHRANE COLLABORATION®

Prophylactic-dose heparin, compared with no heparin:

Symptomatic DVT	RR: 0.48 (95% CI) 0.27 to 0.86)
Death	RR: 0.82 (95% CI 0.53 to 1.26)
Major bleeding	RR: 0.49 (95% CI 0.03 to 7.84)*
Infection	RR: 1.00 (95% CI 0.54 to 1.85);

* Low quality evidence

The use of heparin, compared with VKA:

Thrombocytopenia	RR: 3.73 (95% CI 2.26 to 6.16)
Asymptomatic DVT	RR: 1.74 (95% CI 1.20 to 2.52)

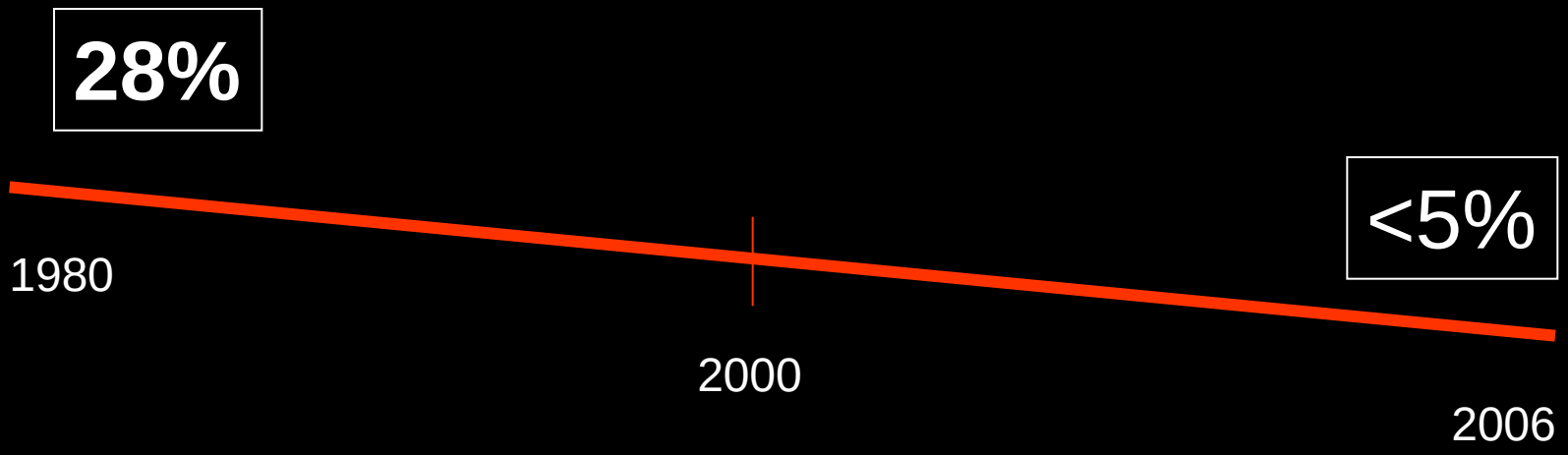
Akl et al., The Cochrane Library 2014

My talk today

- Epidemiology
- Antithrombotic prophylaxis:
  - evidence from literature
  - interpretation of the study results
- Future perspectives

Symptomatic CVC-related thrombosis

Data from studies



Agnelli G. & Verso M. JTH 2006

Hypotesis

1. Overestimation the event rate in earlier studies because the open label design

2. Improved biocompatibility, insertion technique and manteinance of CVCs

3. Patients included in the earlier studies were sicker than those included in recent studies

Agnelli G. & Verso M. JTH 2006

Univariate analysis: covariates

Gender
Age
Body mass index

Cancer site
Cancer histology
Metastases

CVC type & diameter
CVC insertion
CVC tip position
CVC care (time interval)

Chemotherapy

Etichs study: univariate analysis

	All Patients (N=310)			Placebo (N=155)		
	OR	95%CI	P	OR	95%CI	P
Age > 60 yrs	1.5	0.8-2.5	0.2	**2.5**	**1.0-6.2**	**0.04**
Left side CVC	**3.1**	**1.7-5.8**	**<0.001**	**4.7**	**1.9-11.8**	**0.001**
CVC care*						
weekly	**1**			1		
after CHT	**2.4**	**1.2-5.2**	**0.019**	1.9	0.7-4.9	0.2
>2 weekly	**4.6**	**1.3-15.9**	**0.016**	4.5	0.9-22.8	0.073
CVC tip	**6.1**	**2.9-12.8**	**<0.001**	**6.3**	**2.3-17.1**	**<0.001**

* In comparison with weekly care

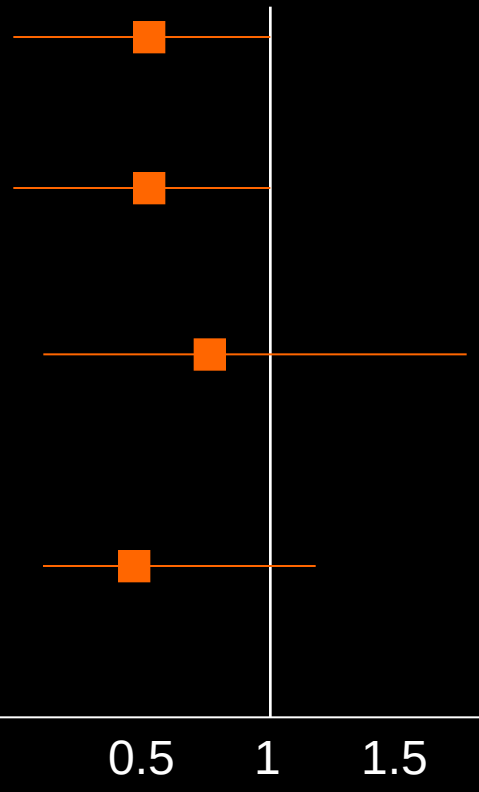
Ethics study: multivariate analysis

	All Patients (N=310)		Placebo (N=155)	
OR	**OR**	**95%CI**	**OR**	**95%CI**
Age > 60 yrs	1.2	0.6-2.5	**2.8**	**1.0-8.0**
Metastases	1.1	0.5-2.6	**4.9**	**1.1-22.8**
Left side CVC	**2.4**	**1.2-4.9**	**4.5**	**1.5-13.3**
CVC care*				
after CHT	1.8	0.8-4.1	1.2	0.3-4.0
>2 weekly	1.5	0.4-6.5	1.9	0.3-13.2
CVC tip	**4.5**	**2.0-9.9**	**4.8**	**1.5-15.4**

* In comparison with weekly care

Ethics study: efficacy of Thromboprophylaxis

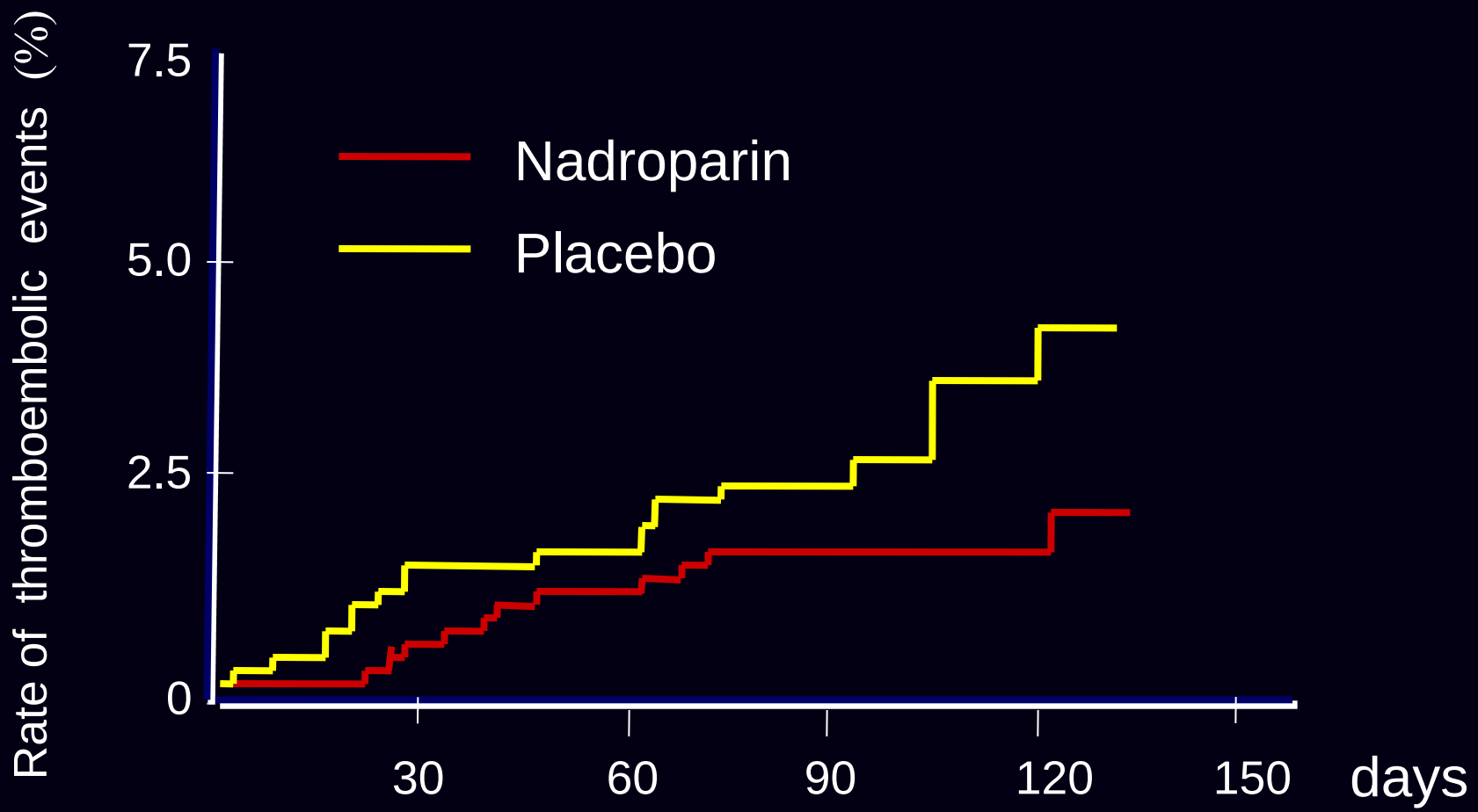
	Enox	Placebo	OR	95%CI
Age > 60y	11/71	20/63	0.5	0.2-1.1
Metastases	14/102	23/86	0.5	0.2-1.1
Inadequate CVC tip	7/10	10/11	0.8	0.2-1.8
Left side CVC	10/40	19/40	0.5	0.2-1.3



My talk today

- Epidemiology
- Antithrombotic prophylaxis:
  - evidence from literature
  - interpretation of the available data
- Future perspectives

Protecht: VTE cumulative event rate



Interim-adjusted p value = 0.024, RRR = 49.6%, NNT 50.5

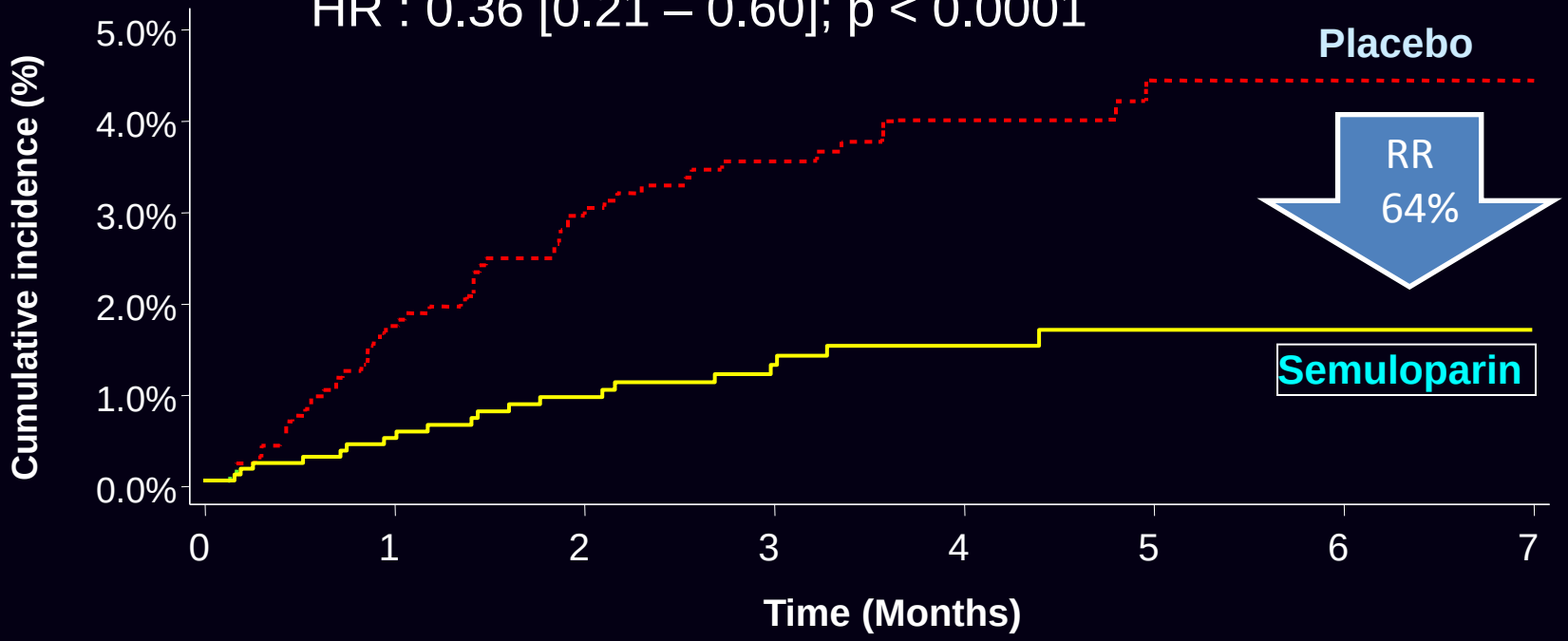
Agnelli et al., Lancet Oncol 2009

Save-Onco: VTE cumulative event rate

Placebo : 3.4% (55/1604)

Semuloparin 1.2% (20/1608)

HR : 0.36 [0.21 – 0.60]; p < 0.0001



Number at Risk

Placebo	1604	1375	1212	985	689	403	201	92
Semuloparin	1608	1410	1227	986	681	384	197	77

HR = hazard ratio

Agnelli et al., N Engl J Med 2012

Conclusions

- The burden of disease linked to CVC-related thrombosis is considerable because the number of CVC inserted.
- Prophylaxis (LMWH or warfarin) is not recommended to prevent CVC-related DVT in cancer patients
- More studies are warranted:
  - to identify subgroups of patients at "particularly high risk" of CVC-related DVT
  - to evaluate the efficacy of thromboprophylaxis in these subgroups of patients

Comments

The antithrombotic prophylaxis is still an open question and there is a room for more research, for the following points.

1. Recent trials were underpowered to detect important differences in clinical thrombosis.
2. Clinical management of patients with CVC-related DVT in not standardized.
3. The burden of illness related to CVC-rlated thrombosis is considerable because the number of CVC inserted.
4. Currently available prophylactic agents are not optimal for cancer patients.

Levine M, JCO 2006

Conclusions

- Different type of patients may have a different need for anticoagulant treatment while CVC is in situ.
- Patients with cancer seem to benefit from antithrombotic prophylaxis.
- Patients with TNP do not seem to benefit significantly from adding heparin to TNP.
- In ICU patients, data are lacking.
- Anticoagulant prophylaxis do not seem to increase the risk of bleeding in all categories of patients with CVC.

Klerk C, Arch Intern Med 2003

Comment

The challenge for the clinician involved in cancer patient care is how to weigh the outcome in the different studies, in order to make a decision for the next patients who gets a CVC catheter in daily clinical practice.

Huisman MV, JTH 2006