



Treatment of Pulmonary Embolism

TF Pulmonary Vascular Pathology

Coordinator
Members

M. Delcroix (Leuven)
G. Brusselle (Gent)
M. Gustin (Liège)
J. Hutsebaut (Bruxelles)
M. Meysman (Brussel)
T. Pieters (Bruxelles)
H. Slabbynck (Antwerpen)
P. Verstraeten (Aalst)



Aims



- ◆ Improve clinical performance through the use of guidelines
- ◆ Adapted to national context
 - translated in both national languages
- ◆ Produced by own specialty society
 - emphasize particularities of PE vs VTE
 - position chest specialists in the care of PE patients



Methodology



- ◆ Formulate exact questions
- ◆ Assess evidence
 - Previous consensus (ACCP 2001, BTS 2003)
 - Recent systematic review (Cochrane, ...)
 - Computer search (Medline, ...)
 - Checking references from articles
- ◆ Studies summarized in evidence tables
- ◆ Determine level of evidence (< discussion)
- ◆ Translate evidence into graded recommendations (< vote)

ACCP 2001 Consensus conference on antithrombotic therapy

Level of evidence	Grade of recommendation	
A: RCTs without important limitations/with consistent results	Strength of recommendation (Clarity of risk to benefit)	
	Grade 1	Grade 2
	Strong (Clear)	Intermediate (Unclear)
B: RCTs with important limitations/with inconsistent results	Strong (Clear)	Weak (Unclear)
C+: Very strong evidence from observational studies	Strong (Clear)	—
C: Observational studies	Intermediate (Clear)	Very weak (Unclear)

ACCP 2003 Lung cancer guidelines

Table 3—Grade of Recommendation Based on Quality of Evidence and Estimate of Net Benefit

Quality of Evidence	Net Benefit			
	Substantial	Moderate	Small/weak	None/Negative
Good	A	B	C	D
Fair	B	B	C	D
Poor	C	C	C or I*	I

*Depending on whether panelists reached consensus or not, this grade could be C or I, respectively.

Topics

- ◆ Particularities of PE vs VTE
- ◆ Anticoagulant therapy
 - Heparin (UFH and LMWH)
 - Coumarines
 - New drugs (factor II and X inhibitors)
- ◆ Thrombolytic therapy
 - Risk stratification
- ◆ Embolectomy (surgical and mechanical)
- ◆ Venous filters
- ◆ Specific problems
 - Pregnancy
 - Elderly
 - Cancer
 - Outpatient treatment
 - Supportive therapy



BVP-SBP

Particularities of PE



- ◆ VTE as a single clinical entity
 - PE and DVT frequently associated
 - Both share many risk factors

BUT

- ◆ Different risk factors
 - Factor V Leiden is a strong risk factor for DVT but not for PE (*Perrier 2000*).
 - thrombus more adherent to the venous wall, lower prevalence of iliofemoral DVT
- ◆ Different natural histories
 - The initial clinical manifestation of VTE (as PE/DVT) strongly predicts the manifestation of a recurrence (as PE/DVT) (*Murin 2002*).
 - PE (+/-DVT) is an independent predictor of reduced survival for up to 3 months after onset compared with DVT alone (*Heit 1999*).
 - Case-fatality rate of recurrent DVT/PE during anticoagulant therapy of 8.8% for patients presenting with DVT and of 26.4% among patients presenting with PE (*Douketis 1998*).
- ◆ Different clinical presentation
 - PE has both hemodynamic (increased RV afterload) and respiratory consequences (hypoxemia)
 - Need for specific interventions
 - Symptoms preferentially orient patients to chest specialists
 - dyspnea (73%), tachypnea (70%), pleural pain (66%), cough (37%), hemoptysis (13%) (*Stein 1991*)
- ◆ Shorter hospital stay in the pneumology dept than in the dept of internal medicine (*Durieux 1989*)



UFH?



1. Do we still need UFH? Which patients?
2. Which dose?
3. What is the optimal duration of therapy?
4. Should we measured heparin level?

UFH

1. Do we still need UFH? Which patients?

- Massive PE
 - ✓ *Konstantinides, NEJM 2002; 347: 1143*
- Peri-operative period
- Peripartum

Grade C

2. Which dose?

- APTT 1.5-2.5 x ULN within 24 hours
 - ✓ *Hull, Arch Intern Med 1992; 152: 1589*
 - ✓ *Basu, NEJM 1972; 287: 324*
 - ✓ *Hull, NEJM 1986; 315: 1109*
 - ✓ *Hull, Arch Intern Med 1997; 157: 2317 and 2562*

Grade A

- Weight-based heparin dosing nomogram
 - ✓ *Raschke, Ann Intern Med 1993; 119: 874*

Grade B

- Infusion rate > 1250 U/hour

Grade B

3. Duration of therapy

- 5 d equivalent to 10 days
- Massive PE: 10 days

Grade B

Grade C

4. Heparin level (0.3 –0.6 IU anti-Xa/ml)

- > 40 000 IU/day
 - ✓ *Basu, NEJM 1972; 287: 325*

Grade B



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LMWH



- ◆ Nadroparin 95 IU/kg bid **Fraxiparine®** *Sanofi-Synthelabo*
190 IU/kg oad Fraxodi®
- ◆ Dalteparin 100 IU/kg bid **Fragmin®** *Pharmacia*
200 IU/kg oad (max 18000 IU)
- ◆ Enoxaparin 100 IU/kg bid **Clexane®** *Aventis*
1 mg/kg bid
1.5 mg/kg oad (max 180 mg)
- ◆ Tinzaparin 175 IU/kg oad **Innohep®** *Leo*

Registered in Belgium



LMWH?



1. Are LMWH better than UFH?
2. Are there differences between LMWH?
3. Do we need a bolus of UFH?
4. Do we need anti-Xa activity monitoring?
5. Long-term treatment with LMWH?



LMWH



1. Are LMWH better than UFH?

- equivalent (as effective and safe)
 - good evidence – substantial benefit (grade A)
- better
 - Less major bleedings and reduced mortality
 - ➔ fair evidence – substantial benefit (grade B)
 - ✓ *Leizorowicz, BMJ 1994; 309: 299 (meta-analysis)*
 - Less HIT and osteoporosis
 - ➔ fair evidence – substantial benefit (grade A)
 - ✓ *ACCP consensus 2001*

LMWH



BVP-SBP

These graded recommendations are NOT classifying LMWH according to their efficacy/safety, but are reflecting the level of evidence available for the indication PE

LMWH



2. Are there differences between LMWH?

- VTE
 - no direct comparison
 - different biochemical and pharmacological properties, dosages and units
 - similar efficacy and safety
 - ✓ *Dolovitch, Arch Intern Med 2000 (meta-analysis)*
- Indication PE
 - Tinzaparin good evidence – substantial benefit (Grade A)
 - Others fair evidence – substantial benefit (Grade B)
- Once daily
 - As safe and as effective as bid
 - ✓ *Dolovitch, Arch Intern Med 2000 (meta-analysis)*
 - Tinzaparin good evidence – substantial benefit (Grade A)
 - Enoxaparin fair evidence – substantial benefit (Grade B)
 - Nadroparin poor evidence – substantial benefit (Grade C)
 - Dalteparin fair evidence – negative benefit (Grade D)

LMWH



2. Are there differences between LMWH?

- Dose reduction
 - Renal insufficiency
 - For all except Tinzaparin
 - ➔ fair evidence – substantial benefit (Grade B)
 - Age
 - Not for Tinzaparin fair evidence – substantial benefit (Grade B)
 - Nadroparin poor evidence – negative benefit (Grade I)
 - Obesity
 - Not for Tinzaparin, Enoxaparin, Dalteparin
 - ➔ poor evidence – substantial benefit (Grade C)
- Neutralization through protamine
 - Depends on molecular weight and degree of sulfonation
 - From 86% (Tinzaparin) to 54% (Enoxaparin) of anti-Xa activity

LMWH



3. Do we need a bolus of UFH?

- fair evidence – no benefit (grade D)
 - ✓ *Hull, Arch Intern Med 2000*



LMWH



4. Do we need anti-Xa activity monitoring?

- Which patients?
 - Renal insufficiency (leading to accumulation)
 - no clear threshold of Cl_{creat} for safety
 - ➔ good evidence – substantial benefit (Grade A)
 - Pregnancy (increased dilution volume and renal clearance)
 - ➔ fair evidence – substantial benefit (Grade B)
- Methodology
 - Measured 4 hours after injection
 - Therapeutic range
 - 0.6-1.0 IU/ml for td
 - 1-2 IU/ml for oad
 - Automated bedside test coming soon (Bayer®)



LMWH



5. Long-term treatment with LMWH

- Which patients?
 - Pregnancy
 - Cancer
 - Recurrence on coumarines
 - CI to coumarines
 - Problematic monitoring
 - ➔ good evidence – substantial benefit (Grade A)
- optimal dosage?
 - ➔ poor evidence – substantial benefit (Grade C)



Coumarines?



- ◆ Which coumarines?
- ◆ What is the optimal intensity of therapy?
- ◆ What is the optimal duration of therapy?
- ◆ Can D-dimers help to predict recurrence?

Coumarines



◆ Which coumarines?

– Plasma half-life

- Acenocoumarol (Sintrom®) 9 hours
- Warfarin (Marevan®)
- Phenprocoumon (Marcoumar®) 42 hours

– Level of evidence

- Warfarin >> Acenocoumarol > Phenprocoumon
- ACCP guidelines don't even mention A and P

◆ Optimal intensity of therapy?

- No loading dose (Grade B)
- INR 2-3 (Grade A)
- Even for prolonged secondary prevention (Grade A)

Long-term secondary prevention



	Recurrent VTE, % per year				Major bleedings, % per year				Death, % per year			
	no	Low	High	p	no	Low	High	p	no	Low	High	p
warfarin												
PREVENT Ridker NEJM 2003 N = 508	7.2	2.6	–	<0.001	0.4	0.9	–	0.25	1.4	0.7	–	0.26
ELATE* Kearon NEJM 2003 N = 738	–	1.9	0.7	0.03	–	1.1	0.9	0.76	–	1.9	0.9	0.09

* Strict exclusion criteria and INR monitoring (≠ real life)

Coumarines



◆ Optimal duration of therapy?

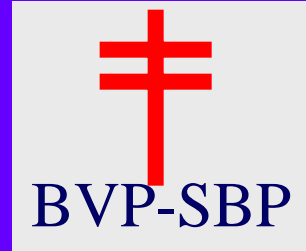
– Determinants

- risk factors
- catch-up phenomenon
 - coumarines 0.7 % per year
 - 6-12 mo after discontinuation 5-10%
 - subsequent years 1-2 % per year
- risk of bleeding
 - Age, previous stroke – peptic ulcer – gastrointestinal bleeding, renal impairment, liver disease, diabetes mellitus, anemia, thrombocytopenia, antiplatelet therapy
- patient preferences

– Recommendations

- Temporary risk factor: 3-6 months (grade A)
- First idiopathic: 6-12 months (grade A)
- Recurrent idiopathic or continuing risk factor: 12 months to indefinite (grade A)

Risk factors for VTE



- ◆ Normal population 1/1000/year

- ◆ Low risk (OR \leq 6): 12 months **(Grade C)**
 - Age > 85-89 y OR 3
 - Second generation pill OR 2
 - Third generation pill OR 5?
 - Hyperhomocysteinemia OR 2-3
 - Anticardiolipin antibodies OR 2-3
 - Increased factor VIII OR 5-6
 - Heterozygous prothrombin mutation OR 3-5
 - Heterozygous factor V Leiden mutation OR 6-9

- ◆ Intermediate risk (10 > OR > 6): years **(Grade C)**
 - Pregnancy OR 10
 - Lupus anticoagulans OR 8-10
 - Heterozygous Protein C/S deficiencies OR 5-10 (20?)

- ◆ High risk (OR > 10): indefinite **(Grade C)**
 - Heterozygous AT deficiency OR 10-40 (70?)
 - Homozygous factor V Leiden mutation OR 50-80
 - Homozygous Protein C/S deficiencies OR >100



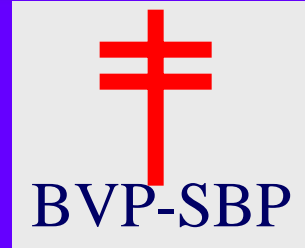


Coumarines



- ◆ Can D-dimers help to predict the risk of recurrent VTE after discontinuation of coumarines?
 - as a global marker of coagulation activation and fibrinolysis
 - D-dimer < 250 ng/ml: cumulative probability of recurrent VTE at 2 years was 3.7 vs 11.7
 - ✓ *Eichinger JAMA 2003*
 - D-dimer < 500 ng/ml: high negative predictive value (95.6%)
 - ✓ *Palareti Thromb Haemost 2002*
- ➔ fair evidence – substantial benefit (Grade B)

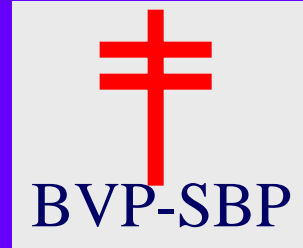
Pentaccharides



- ◆ Fondaparinux (Arixtra®, *Sanofi-Synthelabo*)
 - synthetic indirect FXa inhibitor (acting via AT)
 - registered for prevention of VTE in major orthopedic surgery (early 2003)
 - Matisse-studies
 - ✓ *Buller, NEJM 2003; 349: 1695*
 - fondaparinux 7.5 mg **SC** oad vs adjusted-dose IV UFH (PE)
 - fondaparinux 7.5 mg **SC** oad vs enoxaparin 1 mg/kg SC bid (VTE)
 - **wo BW adaptation** between 50 and 100 kg
 - **equivalent** efficacy and safety
 - ➔ good evidence - moderate benefit/high cost? (**grade B/C?**)



(Xi)-Melagatran



◆ (Exanta®, Astra Zeneca)

- Direct FIIa inhibitor
- Characteristics
 - Oral/SC
 - Larger therapeutical window than coumarines
 - Similar PK than LMWH
 - No drug interaction
 - No dose adaptation for BW or renal function $C_{cl} > 40$ ml/min
- Thrive III-study
 - ✓ *Schulman, NEJM 2003; 349: 1713*
 - prolonged secondary prevention
 - ximelagatran 24 mg **PO** bid vs placebo (prophylactic dose)
 - less recurrences, no increase in bleeding
 - transient elevation of ALT $> 3xULN$ in 6.4 vs 1.2 %
 - ➔ good evidence - substantial benefit (**grade A**)

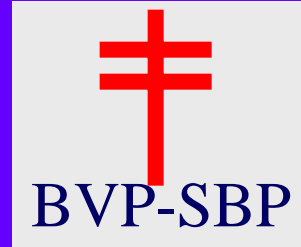
Prolonged secondary prevention



	Recurrent VTE, % per year				Major bleedings, % per year				Death, % per year			
	no	Low	High	p	no	Low	High	p	no	Low	High	p
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THRIVE Schulman NEJM 2003 N = 1233	8.4	1.9	-	<0.001	0.9	0.7	-	NS	0.9	0.7	-	NS

* Strict exclusion criteria and INR monitoring (≠ real life)

Heparin induced thrombocytopenia



- ◆ Lepirudin (Refludan®, *Pharma Logistics*)
 - Recombinant hirudin
 - Direct FIIa inhibitor
 - monitored with APTT
 - HIT treatment
 - bolus 0.12-0,4 mg/kg, infusion 0,15 mg/kg/h
 - SAE: severe anaphylactic shocks
- ◆ Danaparoid (Orgaran®, *Organon*)
 - LMW heparinoid
 - heparan (84%) + dermatan (12%) + chondroitin (4%) sulphates
 - FXa and FIIa inhibitor
 - little effect on APTT, need for FXa assay
 - VTE prevention
 - 750 IU SC bid
- ◆ Fair evidence – substantial benefit (**grade B**)



Thrombolysis?



- ◆ What are the factors predicting mortality?
- ◆ What are the proven advantages?
- ◆ Risk of bleeding
- ◆ Which patients?
- ◆ Which protocol?



PE-related mortality



- ◆ 60-95% in patients presenting with cardiac arrest
- ◆ 14-42% in patients presenting in shock (< 10% of the patients) (ICOPER 1999)
- ◆ ~ 25% in patients with elevated cardiac troponin
- ◆ 5-15% in patients with hypotension
- ◆ ~ 5% in patients with RV dysfunction
- ◆ 1.5% in patients included in prospective trials (Douketis 1998)



Thrombolysis



- ◆ Proven advantages
 - earlier resolution
- ◆ Risk of bleeding
 - Higher for thrombolysis
 - Intracranial hemorrhage (about 2%)
 - Absolute CI
 - Active internal bleeding
 - Recent spontaneous intracranial bleeding



Thrombolysis



◆ Which patients?

– All

→ good evidence - negative benefit (Grade D)

– Shock or hypotension

→ fair evidence – substantial benefit (Grade B)

– RV dysfunction and/or detectable cardiac troponin

• monitored 48 hours in intermediate/intensive care unit

• if deteriorating (respiratory insufficiency or hemodynamical instability)

→ good evidence – moderate benefit (Grade B)



Embolectomy?

- ◆ Which patients?
- ◆ Catheter vs surgical embolectomy?





Embolectomy



- ◆ Which patients?
 - Shock or hypotension
 - Thrombus in transit (RA, RV, PFO)
 - with absolute CI to thrombolysis
 - without response to thrombolysis and maximal inotropy
 - ➔ Poor evidence – substantial benefit (Grade C)

- ◆ Technique
 - Surgical
 - Interventional (suction or fragmentation)
 - Comparable outcomes
 - Local experience and resources
 - ➔ Poor evidence – no benefit (Grade I)



Venous filters?

- ◆ Which patients?
- ◆ Which device?
- ◆ w/wo anticoagulants?



BVP-SBP



Venous filters



◆ Which patients?

- CI to anticoagulants
 - ➔ poor evidence – substantial benefit (Grade C)
- Recurrence under adequate anticoagulation
 - vs switch from coumarines to LMWH
 - ➔ poor evidence – small benefit (Grade I)
- Others (free-floating thrombus, iliofemoral DVT, ...)
 - less PE at 12 days (5 vs 1%), but not at 2 years
 - more recurrent DVT at 2 years (21 vs 12%)
 - no difference in survival
 - ✓ *Decousus NEJM 1998*
 - ➔ good evidence – no benefit (Grade D)

Venous filters



◆ Which device?

➔ poor evidence – unknown benefit (Grade I)



Venous filters



◆ w/wo anticoagulants?

- If possible concomitant anticoagulant therapy should be utilized following filter placement
 - small thrombi can pass through patent filters or through collaterals around obstructed filters
 - direct thrombus extension through the filter is possible
 - Poor evidence – moderate benefit (Grade C)



Pregnancy?

- ◆ Which treatment?
- ◆ Secondary prevention?
- ◆ Need for monitoring?
- ◆ Thrombolysis?



BVP-SBP

Pregnancy



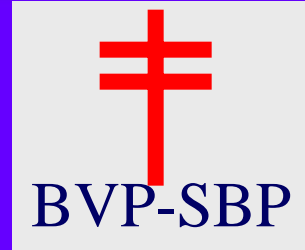
- ◆ LMWHs are first choice therapy
 - ➔ good evidence – substantial benefit (Grade A)
 - discontinued for labour and restarted 4h after delivery for 6 weeks
 - ➔ fair evidence – substantial benefit (Grade B)
- ◆ Secondary prevention
 - prior VTE associated with a transient risk factor
 - ➔ fair evidence – no benefit (Grade D)
 - prior idiopathic VTE w/wo laboratory risk factor
 - ➔ fair evidence – moderate benefit (Grade B)
 - ✓ *Brill-Edwards et al, NEJM 2000; 343: 1339*
- ◆ Monitoring
 - after 1 week and at 28 and 36 weeks gestation
 - therapy (anti-Xa 0.3-1.0 IU/ml), prophylaxis (anti-Xa 0.1-0.4 IU/ml)
- ◆ Thrombolysis
 - reasonable risk for the mother and the fetus (streptokinase)
 - ➔ fair evidence – substantial benefit (Grade B)



Elderly?

- ◆ LMWH
 - Dose-adaptation?
- ◆ Coumarines
 - Bleeding?
- ◆ Thrombolysis

Elderly



◆ LMWH

- No dose reduction
- ➔ fair evidence – substantial benefit (Grade B)
- ✓ *Mismetti 1998 (nadroparin)*
- ✓ *Siguret 2000, Pautas 2002 (tinzaparin)*

◆ Coumarines

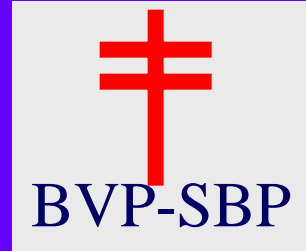
- INR 2-3: safe (intracranial bleeding)
- ➔ good evidence – substantial benefit (Grade A)

◆ Thrombolysis

- Risk not increased by age
- ➔ fair evidence – substantial benefit (Grade B)



Cancer?



- ◆ Should cancer patients be treated differently?
 - efficiency
 - anti-tumoral effect

Cancer



- ◆ LMWH > coumarines
 - Coumarin effect is rather unpredictable because of drug interactions
 - Reduction in recurrent VTE
 - ✓ *Canthinox Meyer 2002, CLOT Lee 2003 and LITE Hull 2002*
 - ➔ Good evidence – substantial benefit (Grade A)
- ◆ Anti-tumoral effect?
 - ✓ *FAMOUS Kakkar 2002*
 - ➔ Poor evidence – small benefit (Grade C)



Outpatient treatment?



- ◆ Is outpatient safe for PE?
- ◆ Which patients can be early discharged?



Outpatient treatment



- ◆ Is outpatient safe for PE?
 - poor evidence – small benefit (Grade I)
- ◆ Which patients can be early discharged (48h)?
 - Wicki clinical score ≤ 2
 - Absence of RV dysfunction
 - Undetectable levels of cardiac troponin
 - ➔ fair evidence – substantial benefit (Grade B)



Supportive therapy



- ◆ Fluid loading
 - poor evidence – small benefit (GRADE I)
- ◆ Inotropics as dobutamine, nor- and epinephrine may be used in hypotensive patients
 - poor evidence – moderate benefit (GRADE C)
- ◆ NO
 - poor evidence – moderate benefit (GRADE C)
- ◆ ECMO
 - poor evidence- moderate benefit (GRADE C)