Risque thromboembolique:

Le sujet âgé et / ou insuffisant rénal

Marc Lambert
Service de Médecine Interne
CHRU LILLE

14ème JLAR - 22 février 2007

Le patient âgé, un patient à haut risque thrombotique

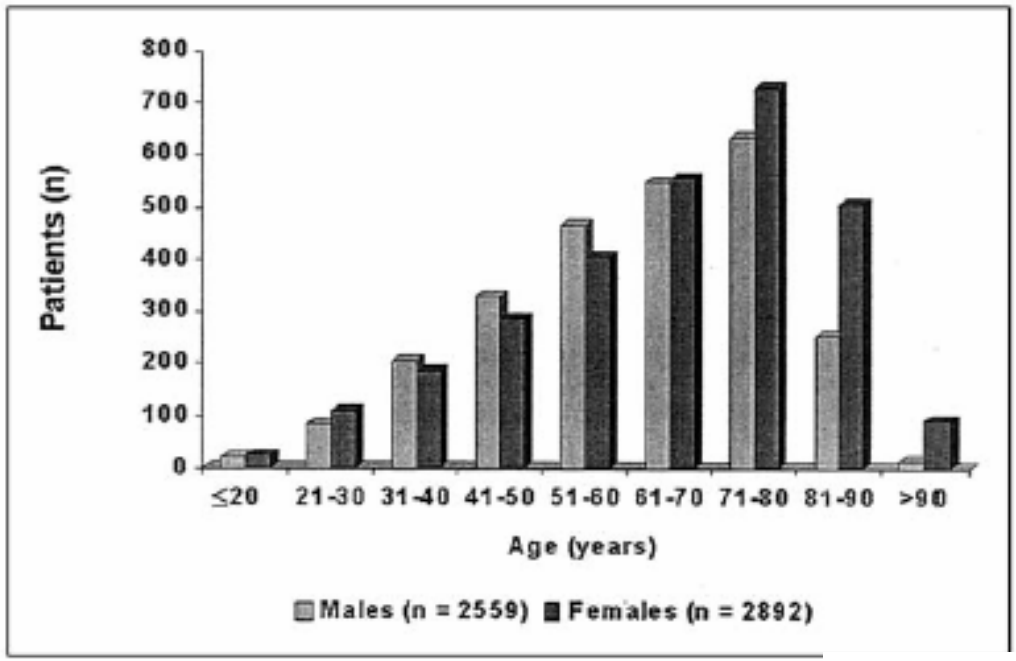
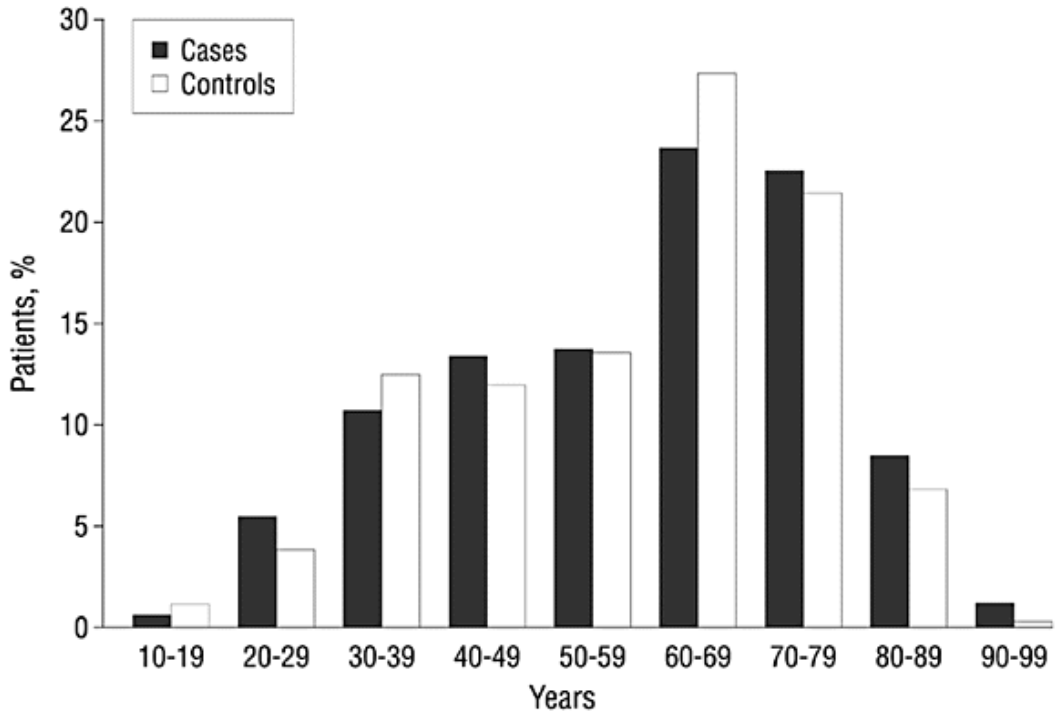


FIGURE 1. Distribution of patients by age and gender

Samama MM. Arch Intern Med 2000.

Golhaber SZ. et al



Ratio evt thrombotique par rapport à la tranche d'âge 20-29 ans

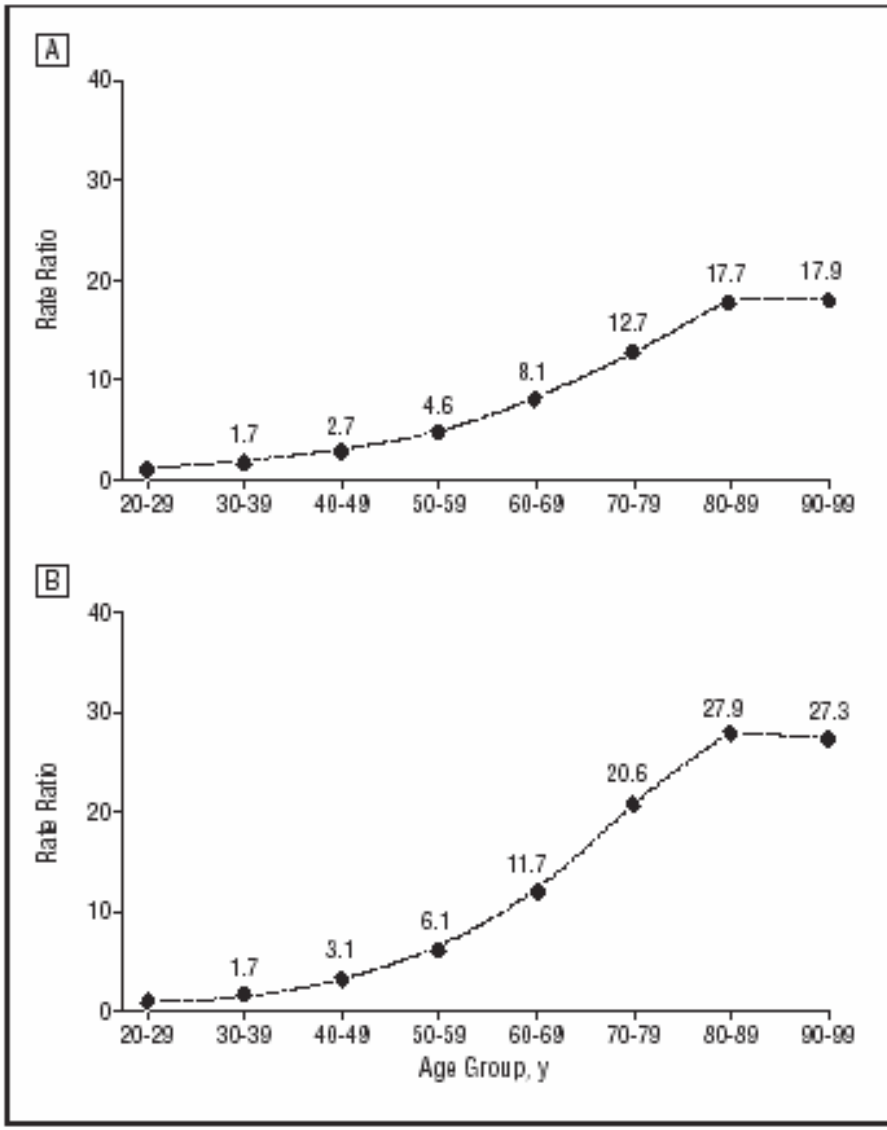


Figure 6. Rate ratios for the diagnosis of deep venous thrombosis (DVT) and pulmonary embolism (PE) were averaged over 21 years. A, The rate ratios for the diagnosis of DVT increased exponentially (95% confidence intervals were too narrow to display). B, The rate ratios for the diagnosis of PE increased exponentially (95% confidence intervals were too narrow to display).

Stein PD et al. Arch Intern Med 2004

Epidémiologie

- TVP: 1 % des plus de 75 ans.

  Heit JA et al. Epidemiology of VTE in the community. Thromb Haemost 2001.

- 15 % des patients en soins de suite.

  Bosson et al. Arch Int Med 2003

- Maladie plus grave: 39 % de mortalité à 1 an

  Kniffin WD et al. Arch Int Med 1994.

- Pathologie tumorale sous jacente

Facteurs de risque médicaux de Thrombose veineuse

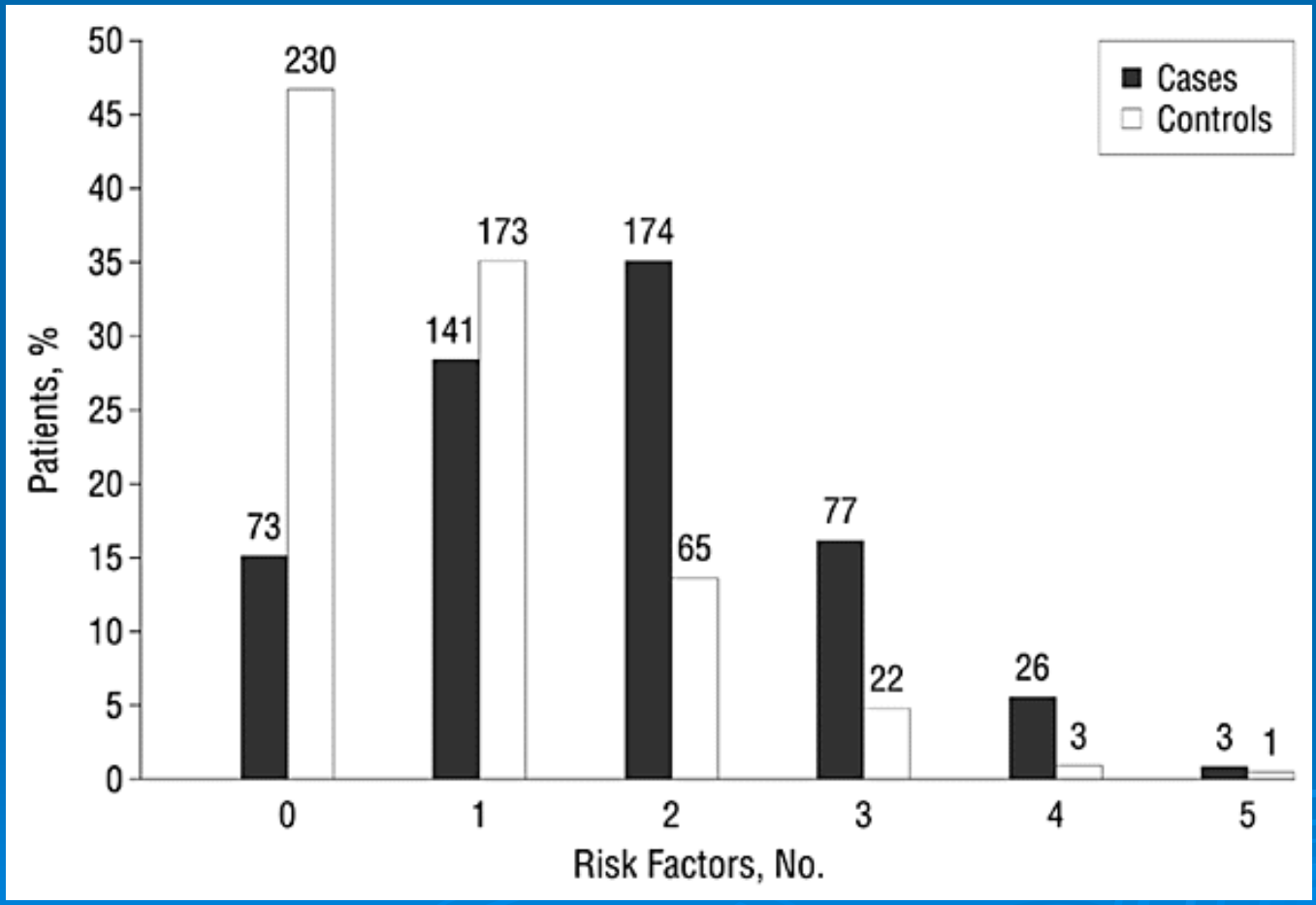
Table 1. Risk Factors in Descending Order of Importance of a Medical Study Population*

Risk Factors	Case Patients, No. (%)	Control Patients, No. (%)	Odds Ratio (95% CI)	*P*
Intrinsic factors				
History of DVT or PE	105 (21.3)	12 (2.4)	15.6 (6.77-35.89)	<.001
Venous insufficiency	346 (70.0)	203 (41.1)	4.45 (3.10-6.38)	<.001
Chronic heart failure	51 (10.3)	22 (4.5)	2.93 (1.55-5.56)	.001
Obesity†	72 (14.8)	34 (7.0)	2.39 (1.48-3.87)	<.001
Standing position >6 h/d	104 (38.7)	69 (31.9)	1.85 (1.12-3.06)	.02
History of >3 pregnancies‡	54 (16.5)	32 (9.8)	1.74 (1.06-2.87)	.03
Triggering factors				
Pregnancy‡	8 (2.4)	1 (0.3)	11.41 (1.40-93.29)	.02
Violent effort or muscular trauma	39 (7.9)	5 (1.0)	7.59 (2.95-19.53)	<.001
Deterioration in general condition	31 (6.3)	6 (1.2)	5.75 (2.20-15.01)	<.001
Immobilization§	38 (8.0)	10 (2.0)	5.61 (2.30-13.67)	<.001
Long-distance travel	62 (12.6)	31 (6.3)	2.35 (1.45-3.80)	<.001
Infectious disease	95 (19.2)	63 (12.8)	1.95 (1.31-2.92)	.001

**CI indicates confidence interval; DVT, deep vein thrombosis; and PE, pulmonary embolism.*
†Obesity was defined as a body mass index of more than 30 kg/m^2.
‡In 325 women.
§Total confinement to bed or to bed and armchair.

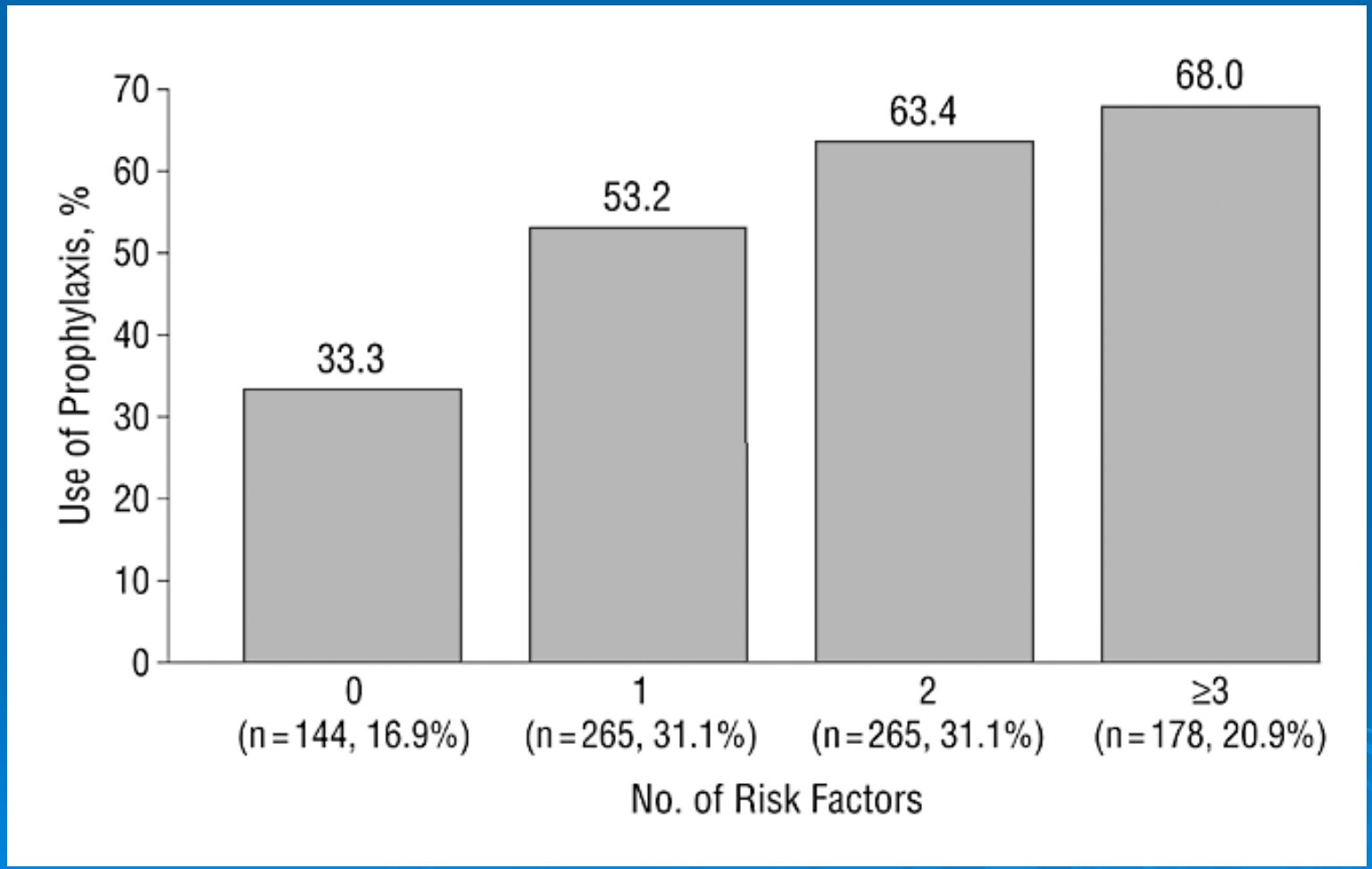
Samama MM et al. Arch Intern Med 2000.

Nombres de facteurs de risque thrombotiques



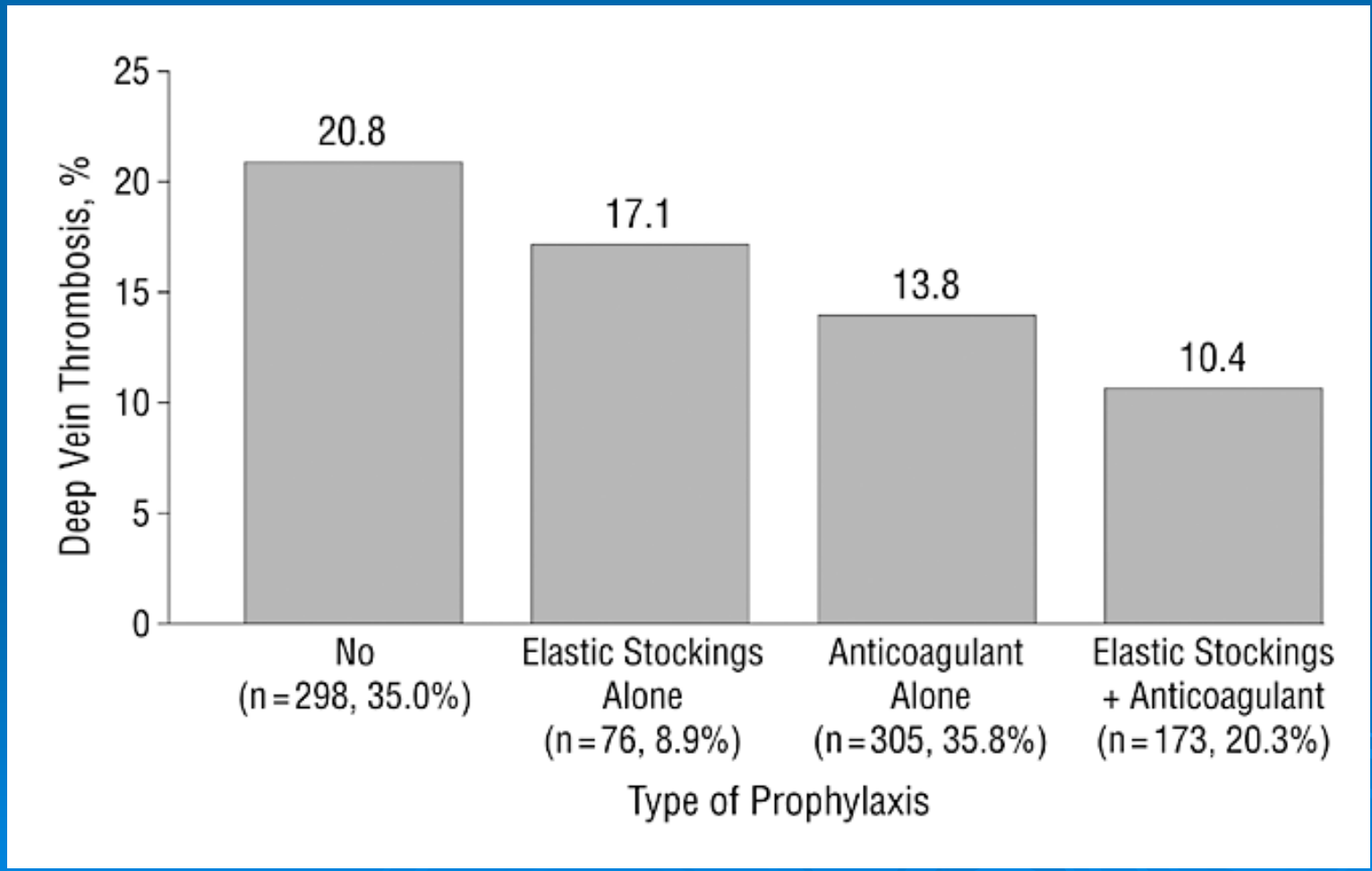
Samama MM et al. Arch Intern Med 2000.

Utilisation d'une prophylaxie en fonction du nombre de FDR de thrombose veineuse (852 patients de plus de 65 ans en moyen séjour)



Bosson JL et al. Arch Intern Med 2003

Type de prévention et fréquence de la TVP



Bosson JL et al. Arch Intern Med 2003

Quel type de prévention ?

- Déambulation
- Contention
- HBPM (Geerts WH. Chest 2004; 126: 338S-400S)
- **Réduction significative de la fréquence des TVP**

Intérêt des HBPM en fonction de l'âge

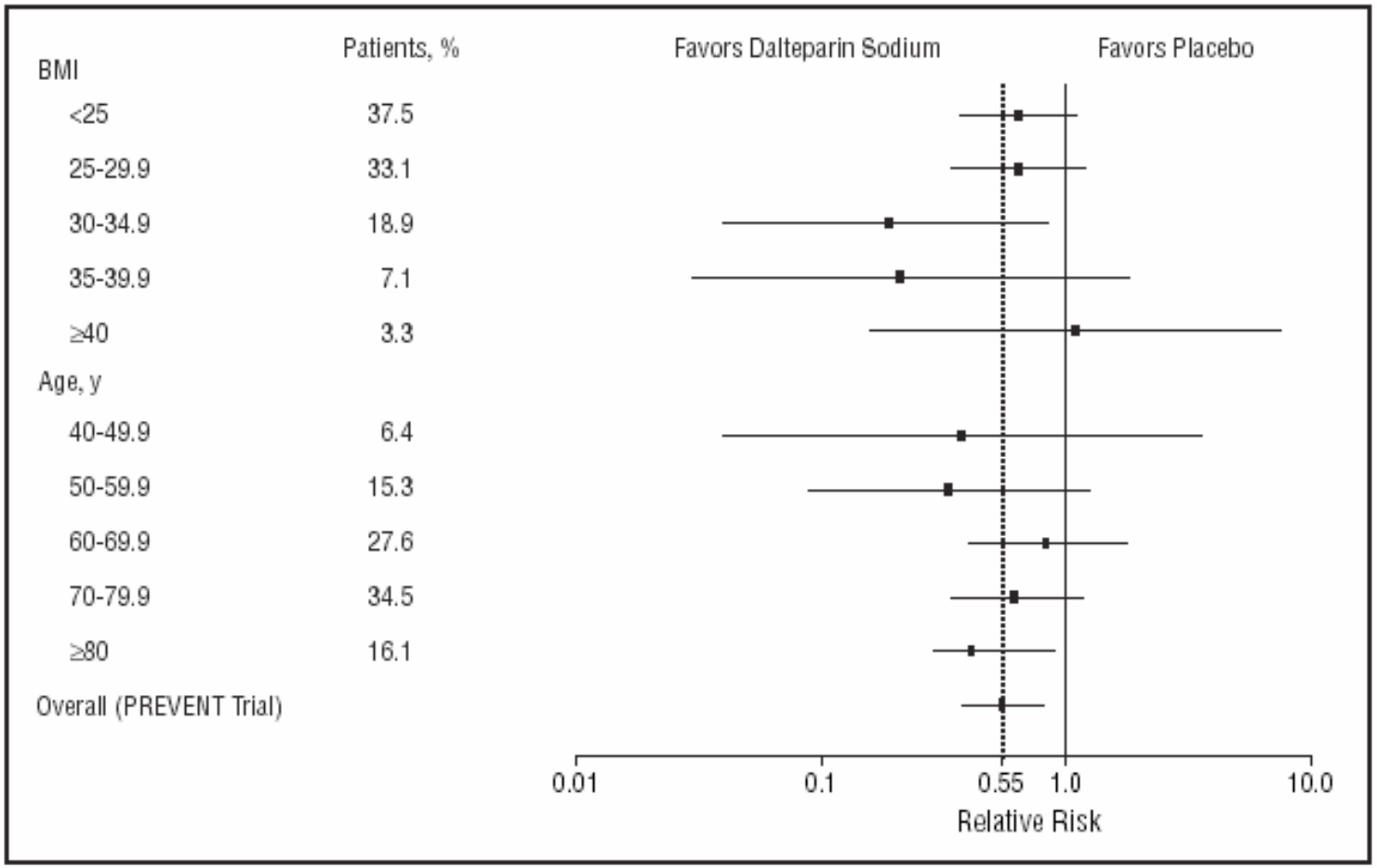


Figure. Effect of dalteparin sodium on prevention of the primary end point in body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) and age subgroups, presented as relative risk (logarithmic axis) and 95% confidence intervals.

Kucher N et al. Arch Intern Med 2005.

A Prospective Registry of 5,451 Patients With Ultrasound-Confirmed Deep Vein Thrombosis

Samuel Z. Goldhaber, MD, and Victor F. Tapson, MD, for the DVT FREE Steering Committee*

- 3894 patients sans prophylaxie
  - 2295 patients non chirurgicaux

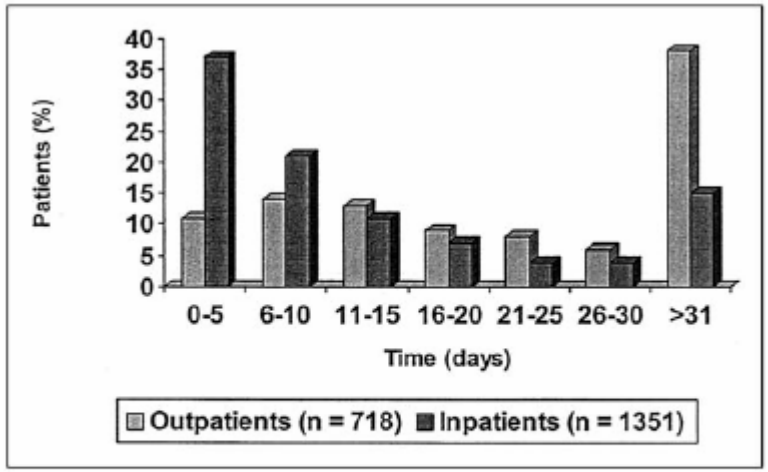


FIGURE 3. Time from most recent surgery to diagnosis of DVT by patient status at the time of DVT diagnosis. Data are missing for 25 patients.

Golhaber SZ. et al. Am J Cardiol 2004

Le patient âgé, un patient à haut risque hémorragique

Hémorragies et héparines

Table 3. Summary of Meta-Analysis Results*

Variable	Patients	Summary Odds Ratio (95% CI)†	Summary Absolute Risk Reduction (95% CI)‡	NNT	Frequency in UFH Group	Frequency in LMWH Group§
	n		%	*n*	*n/n (%)*	
Major bleeding (fixed-effects model)	3674	0.57 (0.33 to 0.99)‖	0.61 (−0.04 to 1.26)	164	35/1853 (1.9)	20/1821 (1.1)
Major bleeding (random-effects model)	3674	0.71 (0.40 to 1.27)	0.66 (−0.09 to 1.41)	151	35/1853 (1.9)	20/1821 (1.1)
Recurrent thromboembolism	3566	0.85 (0.63 to 1.14)	0.88 (−0.48 to 2.24)	114	97/1792 (5.4)	82/1774 (4.6)
Death (overall)	3566	0.71 (0.53 to 0.94)‖	1.65 (0.36 to 2.94)‖	61	122/1792 (6.8)	88/1774 (5.0)
Death						
Due to RTE	3566	0.75 (0.31 to 1.79)	0.21 (−0.28 to 0.71)	468	12/1792 (0.7)	9/1774 (0.5)
Due to major bleeding	3566	0.67 (0.11 to 4.00)	0.15 (−0.20 to 0.51)	656	3/1792 (0.2)	2/1774 (0.1)
Due to RTE or major bleeding	3566	0.73 (0.33 to 1.60)	0.22 (−0.34 to 0.77)	460	15/1792 (0.8)	11/1774 (0.6)
In patients with cancer	279	0.57 (0.31 to 1.03)	9.75 (0.34 to 19.16)‖	10	38/147 (25.9)	22/132 (16.7)

* All results are from the fixed-effects model unless otherwise noted. LMWH = low-molecular-weight heparin; NNT = number needed to treat; RTE = recurrent thromboembolism; UFH = unfractionated heparin.
† A summary odds ratio less than 1.0 favors LMWH; a summary odds ratio greater than 1.0 favors UFH.
‡ A summary absolute risk reduction greater than 0.0 favors LMWH; a summary absolute risk reduction less than 0.0 favors UFH.
§ Simple pooling of results from individual patients was not used to calculate summary odds ratios or absolute risk reductions.
‖ $P < 0.05$.

Gould MK et al. Ann Intern Med 1999

Facteurs cliniques majorant le risque d'accidents hémorragiques chez le sujet âgé.

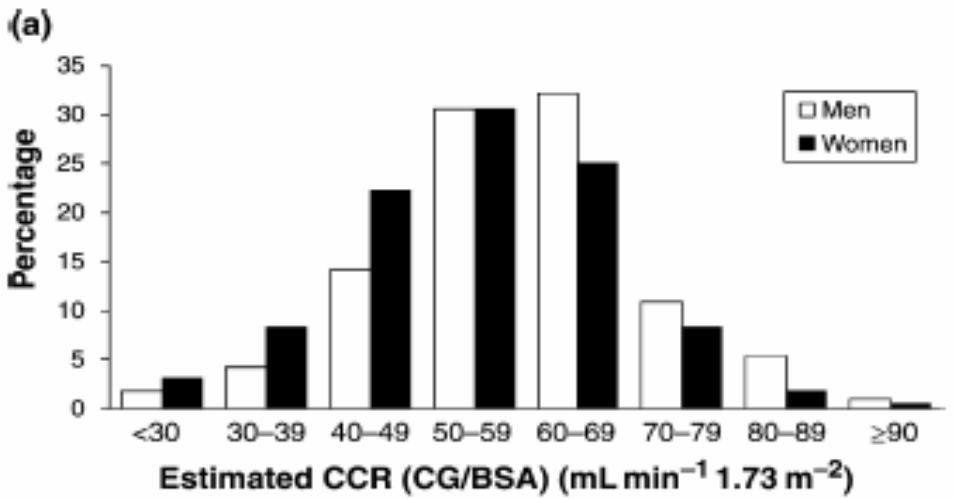
- Age > 75 ans
- Utilisation de médicaments associés potentialisant le risque
- Observance médicamenteuse insuffisante
- HTA non contrôlée (TAs > 180 mmHg ou TAd > 100 mmHg)
- Saignement récent : hémorragie digestive, hématome intracranien récent (datant de 1 à 3 mois)
- Antécédent de saignement digestif
- "Malaises et Chutes" mais…certainement surestimé!
- Alcoolisme (aigu ou chronique)
- Néoplasie
- Cardiopathie évoluée
- Insuffisance rénale sévère

La réduction néphronique

- **Élimination essentiellement rénale des HBPM**
  - **Risque de surdosage et/ou accumulation chez l ’insuffisant rénal**
  - **Unités gériatriques :**
    - **Clairance de Créatinine <30 mL/min chez 20 % des patients hospitalisés**

Finlandais

Age moyen 74 ans



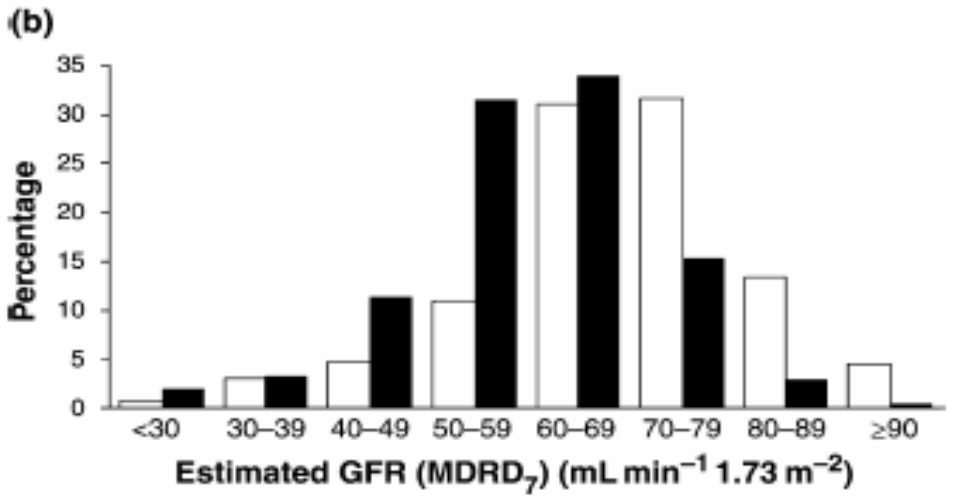
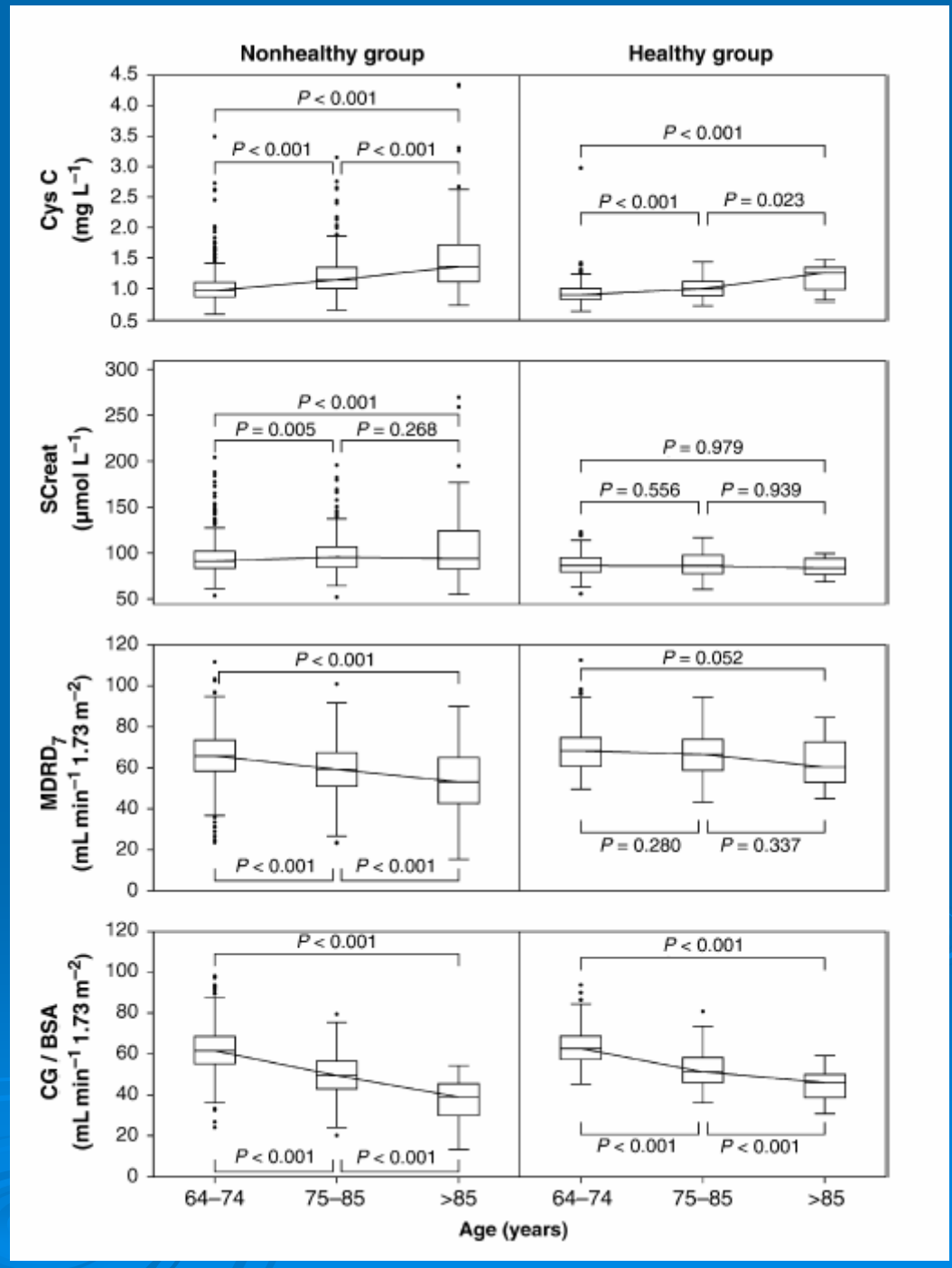


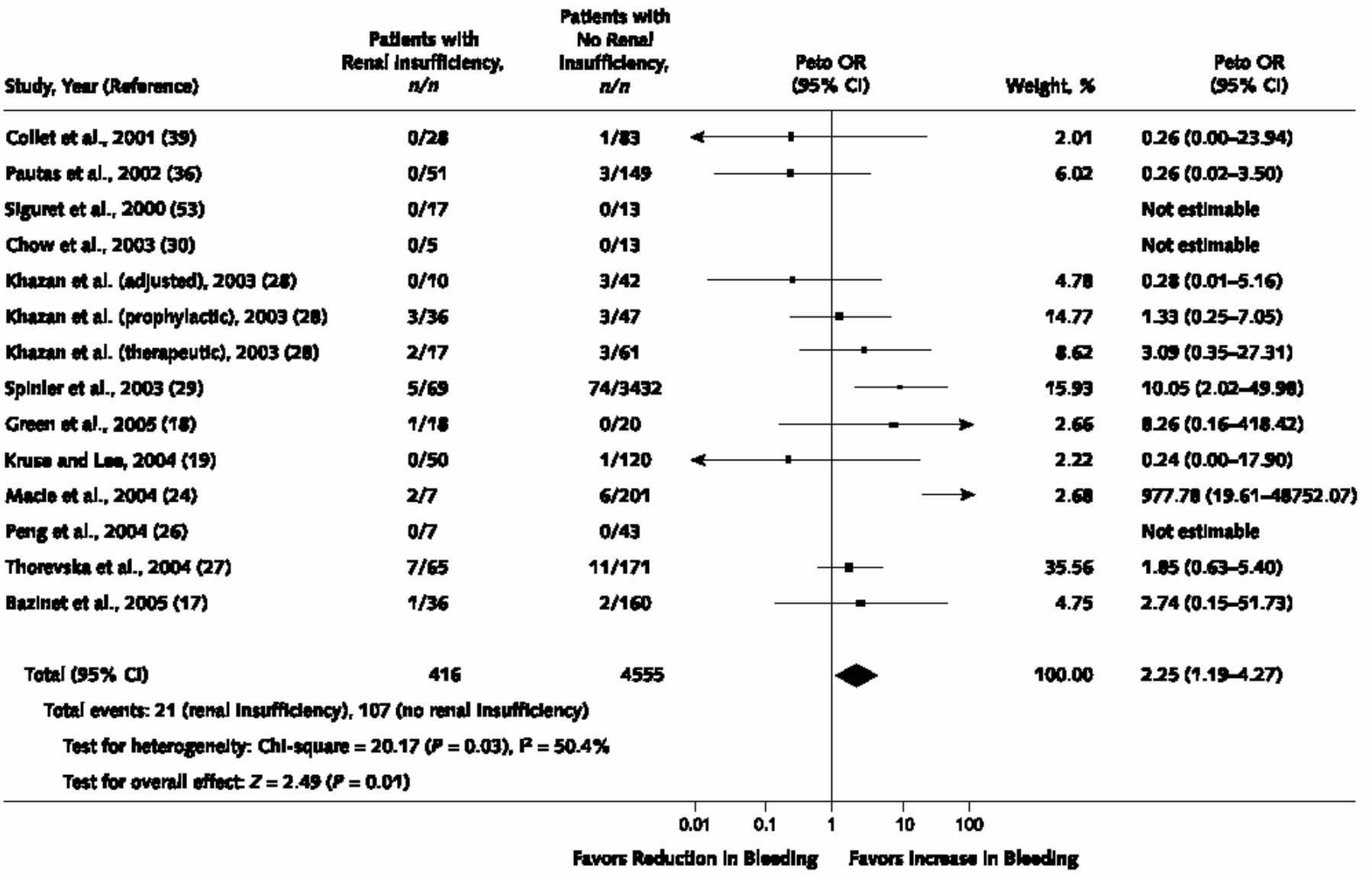
Fig. 1 (a) Distribution of estimated creatinine clearance (CCR) calculated by the Cockcroft-Gault equation adjusted for body surface area (CG/BSA) by gender ($n = 1246$). (b) Distribution of estimated glomerular filtration rate (GFR) calculated by the Modification of Diet in Renal Disease Study equation 7 (MDRD$_7$) by gender ($n = 1246$).

Wasen E et al. J Intern Med 2004



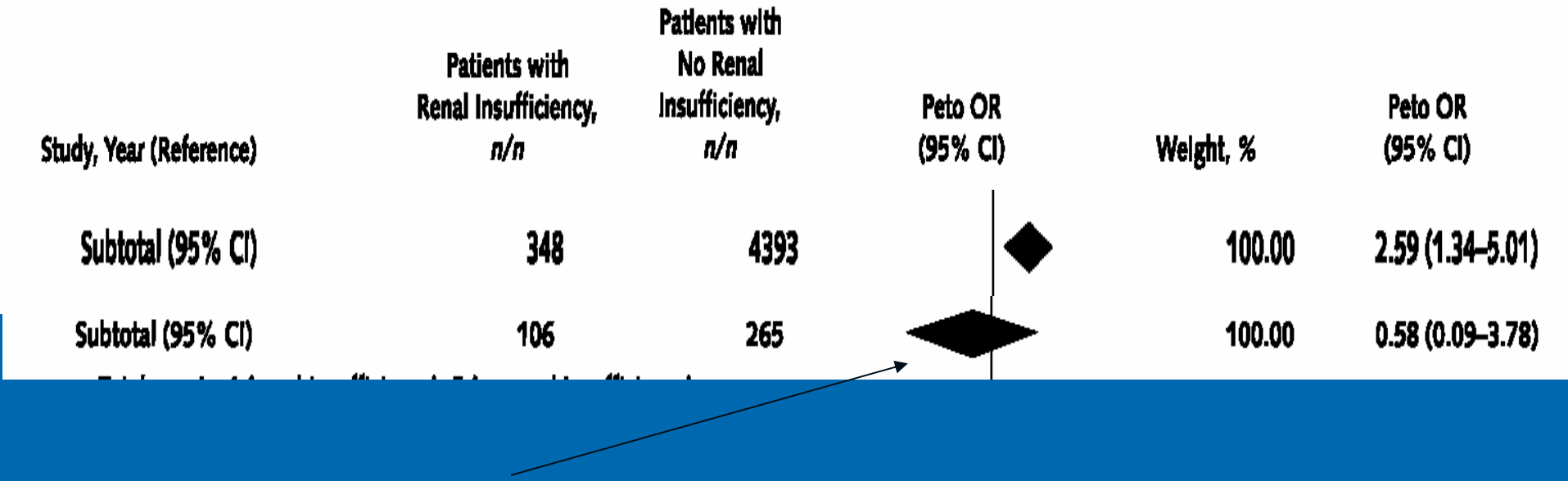
Wasen E et al. J Intern Med 2004

Figure 2. Peto odds ratio (*OR*) of major bleeding events in patients with severe renal insufficiency (creatinine clearance ≤30 mL/min) compared with patients without renal insufficiency (creatinine clearance >30 mL/min).



Lim W. Ann Intern Med 2006

Avec l'Enoxaparine



Dose ajustée à la clairance de la créatinine ou à l'anti-Xa

Lim W. Ann Intern Med 2006

Avec la Tinzaparine

Tinzaparin								
Pautas et al., 2002 (36)	Prospective cohort; C	Not funded	ACS, AF, VTE, other	20–34 35–49 50–64 ≥65	51 60 44 45	175 IU/kg daily	0 1 (1.7) 0 2 (4.4)	30 d; no loss to follow-up
Siguret et al., 2000 (53)	Prospective cohort; C	NS	AF, VTE, other	20–29 30–39 40–49 ≥50	8 9 6 7	175 IU/kg per d	0 0 0 0	10 d; no loss to follow-up

Lim W et al. Ann Intern Med 2006

Pautas E et al. Drug Saf. 2002

- 200 sujets âgés
  - 85 ans, moyenne Clairance Créatinine 51mL/min
  - Tinzaparine 175UI / kg / j
  - durée de traitement 19 jours
- 3 saignements majeurs (1,5%), dont 1 fatal
  - Même taux de saignement que chez sujets plus jeunes (études phase III)
- pas de corrélation entre antiXa, âge et ClCr

Cestac P et al. Drug Saf. 2003

- **334 patients hospitalisés en gériatrie**
  - **age moyen 72.5 ans**
- **450 prescriptions d'HBPM**
  - **Enoxaparine ou tinzaparine**
- **Effets secondaires: 10.5 %**
  - **Saignements: 15 evts**
- **Analyse multivariée du risque hémorragique:**
  - **RR 1.34 (par 10 ml / mn de diminution de clairance de créatinine)**
  - **RR 2.8 si CL CR < 20 ml/mn**

RISQUE D'ACCUMULATION **=> I.R.I.S.**

Mahe I et al. Drugs Aging 2007

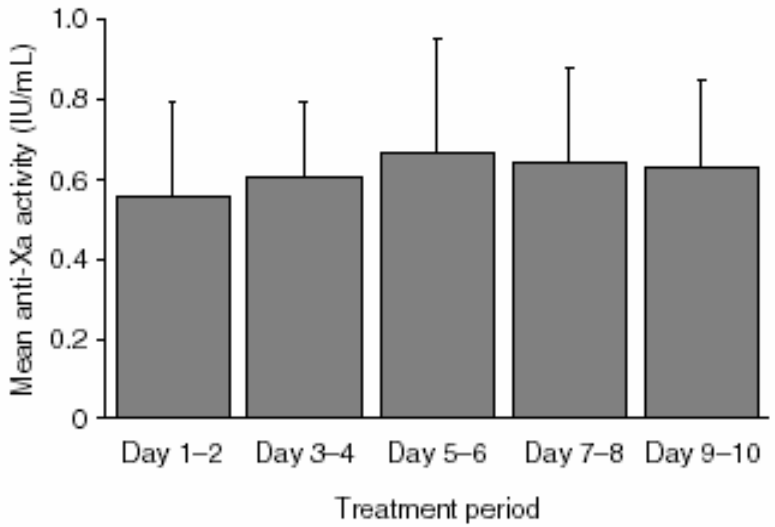


Fig. 1. Mean anti-Xa activity levels over the 10-day treatment period in the whole population (n = 125).

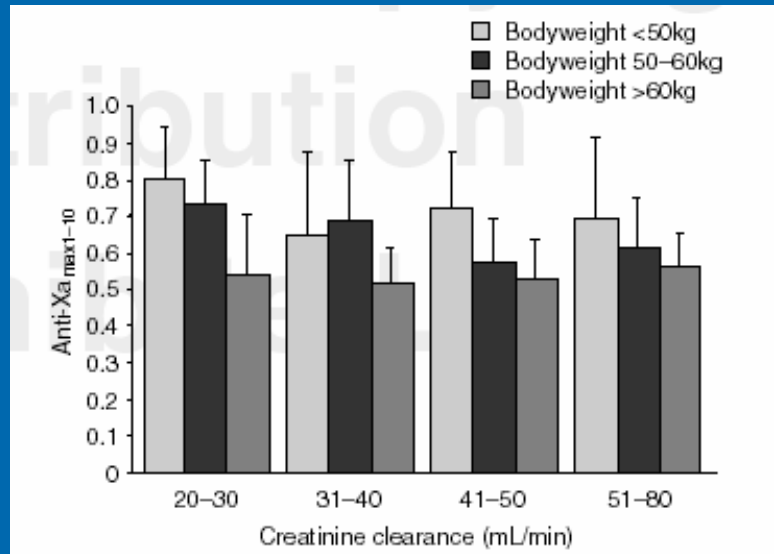


Fig. 4. Relationship of maximum anti-Xa activity throughout the 10-day treatment period (anti-$Xa_{max1-10}$) to bodyweight and creatinine clearance.

Table II. Characteristics of patients with bleeding events

Event	Sex	Age (y)	Occurrence (treatment day)	Bodyweight (kg)	Creatinine clearance (mL/min)	Last anti-Xa value available (IU/mL)	Concomitant treatment
Haematemesis	M	90	9	60	33	0.53 on day 4	
Haematemesis	F	100	9	52	19	0.67 on day 8	Acetylsalicylic acid (aspirin)
Haematemesis	M	79	5	68	57	0.39 on day 2	
Haemothorax	F	97	5	49	19	0.92 on day 1	
Melaena	M	91	1	50	33	0.55 on day 1	

125 patients > 75 ans, prevention médicale enoxaparine 4000 ui

Avec le Fondaparinux

Table 3 Bleeding complications during study treatment of older (≥60 years) medical patients randomised to the anticoagulant fondaparinux or placebo

Bleeding complication	Fondaparinux group (n=425)	Placebo group (n=414)
Major bleeding:		
Fatal	0	0
Requiring surgical intervention	0	0
In a critical location	0	0
Overt bleeding plus a decrease in haemoglobin concentration ≥20 g/L (<48 hours) or transfusion of ≥2 units	1	1
Total No (%)	1 (0.2)	1 (0.2)
Minor bleeding	11 (2.6)	4 (1.0)

Cohen AT et al. BMJ 2006

½ vie sujet standard: 17 h
½ vie chez le sujet âgé: 28 h

Samama MM et al. Thromb Res 2003

En USI

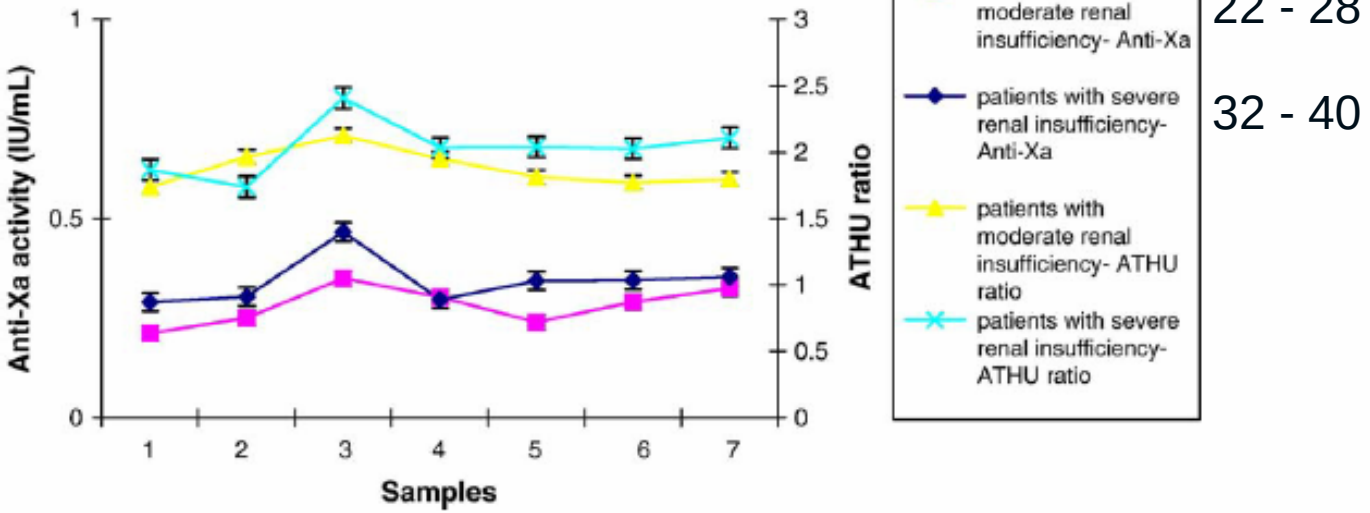
Table 2 Laboratory results of study patients

Pt	ICU LOS (d)	IBW (kg)	CrCl (mL/min)			Trough above detection threshold (U/mL)		Peak (U/mL)		
			Mean	Range	n	Value	n	Mean	Range	n
1	7	57	52	37-63	6	0.18	1			0
2	8	63.8	64	50-73	6	–	6			0
3	4	47.8	79	77-80	2	–	2			0
4	8	77.6	71	46-92	9	–	5			0
5	10	77.6	160	124-199	10	–	6			0
6	12	54.1	82	72-91	11	–	9			0
7	31	47.8	57	42-83	27	–	16			0
8	10	47.8	64	45-81	10	–	10			0
9	30	68.4	174	142-201	29	–	20	0.27	<.1-.51	4
10	25	70.7	26	19-41	24	–	16	.33	.33	1
11	19	52.4	60	36-84	17	–	15	.20	<.1-.37	18
12	54	66.1	100	45-151	45	–	12	.42	.33-.49	10
13	5	70.5	208	201-217	4	–	3	.22	.19-.27	3
14	9	77.6	71	66-79	9	–	4	<.1	<.1	4
15	22	57	57	42-87	19	–	15	.20	<.1-.35	14
16	14	77.6	146	127-176	14	0.19	10	.22	<.1-.32	12
17	22	63.2	141	97-188	17	0.53	20	.40	.22-.66	20
18	4	54.7	40	38-42	3	–	2	.32	.28-.39	3
19	26	59.3	137	80-210	25	–	21	.42	.21-.57	24
Total	320	62.6	97	19-218	287		185	0.30	<.1-0.66	113

We present the creatinine clearance, trough and peak anti-Xa levels of study patients. Pt indicates patient; LOS, length of stay; IBW, ideal body weight; CrCl, creatinine clearance.

19 patients, score APACHE II = 23.5, dalteparine 5000 ui

Rabbat CG et al. J Crit Care 2005.



22 - 28

32 - 40

Fig. 1 Anti-Xa ATHU test measurements in ICU patients with moderate or severe renal insufficiency after subcutaneous administration of dalteparin.

10 patients en USI, 72 ans +/- 11, dalteparine 5000 ui.

Kani C et al. J Crit Care 2006

Comment améliorer la sécurité de prescription ?

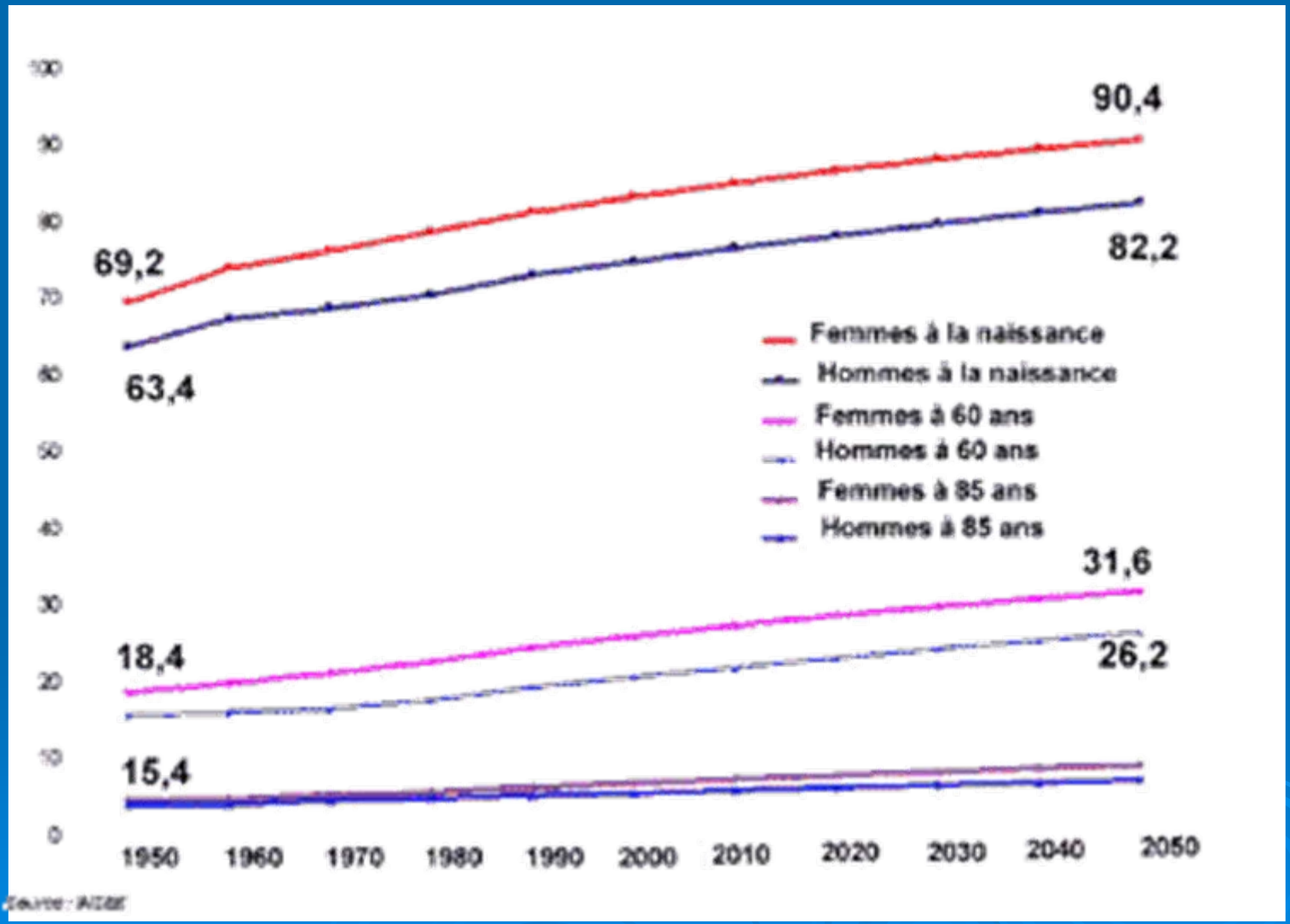
- Préférer les HNF ?
  - Risque hémorragique similaire ?
  - Modification des modalités de prise en charge

- Ajuster sur l'anti - Xa ou la clairance de créatinine (Enoxaparine, Tinzaparine)

En pratique

- **Poids du patient**
- **Clairance de créatinine**
  - **Clairance de Créatinine <30 mL / min**
- **Réduire les durées de traitement à moins de 10j**
- **Interactions médicamenteuses**

Espérance de vie



Merci de votre attention

m-lambert@chru-lille.fr