Thromboembolie – der leise Killer

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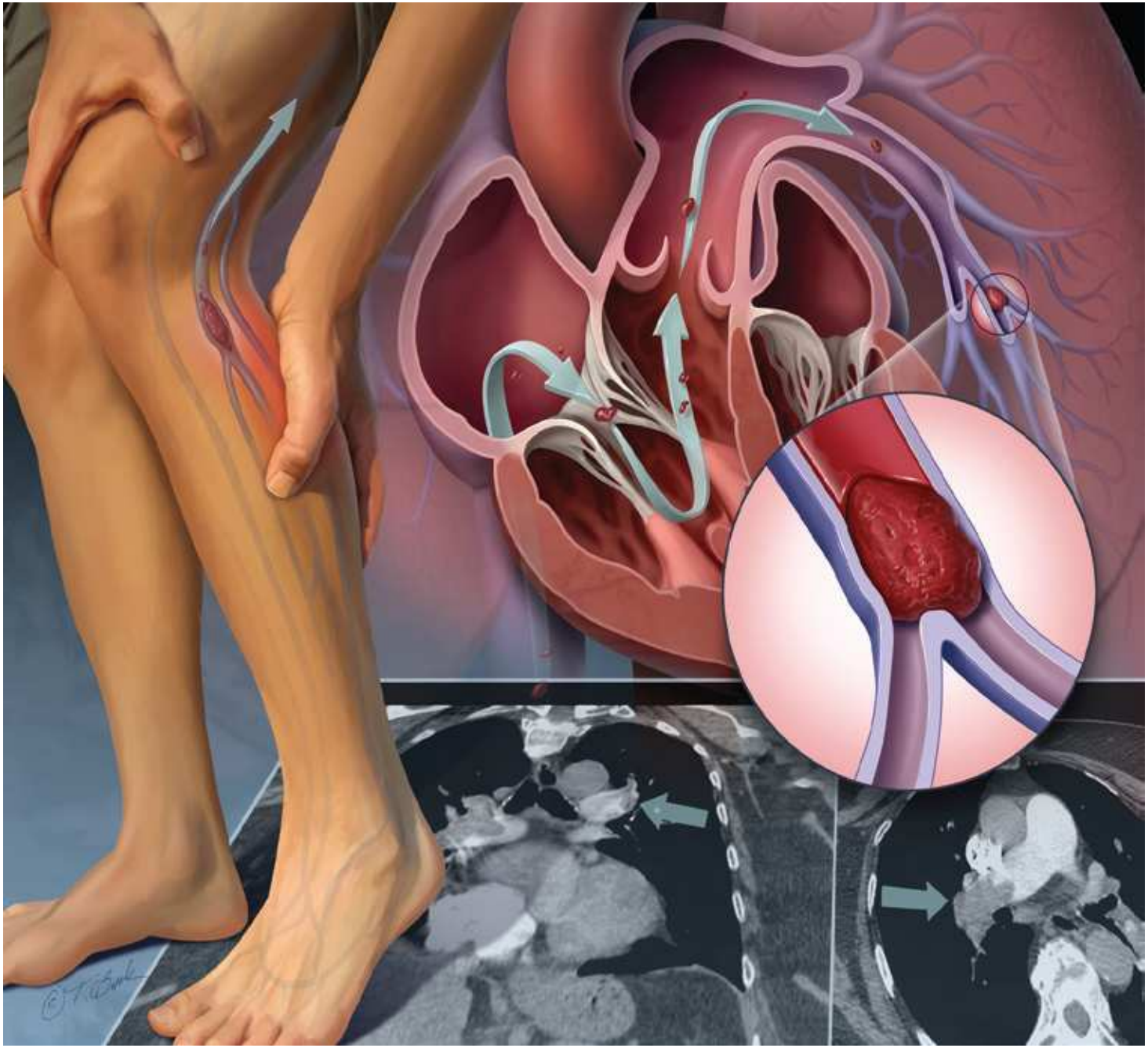


Incidence rates per 1000 population per year according to age category

Author and year	Global region	Country	Age 40 –49 years	Age 50 –59 years	Age 60 –69 years	Age 70 –79 years	Age ≥ 80 years
Kroger *et al.* 2010 [40]	Western Europe	Germany	0.30 male[*] 0.28 female	–	1.24 male 0.94 female	–	3.45 male 3.72 female
Naess *et al.* 2007 [19]	Western Europe	Norway	0.20 male[†,‡] 0.17 female	0.72 male 0.72 female	1.14 male 0.93 female	1.85 male 1.45 female	3.73 male 3.84 female
Oger *et al.* 2000 [21]	Western Europe	France	1.52 male[§] 1.05 female	–	5.33 male 4.53 female	–	10.81 male 12.04 female
Nordstrom *et al.* 1992 [22]	Western Europe	Sweden	0.69 male[‡] 0.97 female	2.85 male 1.03 female	3.27 male 2.17 female	5.64 male 4.29 female	7.65 male 8.22 female
Tagalakis *et al.* 2013 [24]	North America	Canada (Quebec)	0.83	1.42	2.57	4.41	6.85
Yusuf *et al.* 2012 [9]	North America	USA	1.43	2.00	3.91	7.27	11.34
Silverstein *et al.* 1998 [30]	North America	USA	0.90 male[†] 0.45 female[†]	0.76 male 0.83 female	1.63 male 1.69 female	6.46 male 3.22 female	9.84 male 8.49 female
Anderson *et al.* 1991 [32]	North America	USA	0.17[‡]	0.43	1.19	2.32	2.91
Lee *et al.* 2010 [37]	East Asia	Taiwan	NR[¶]	NR[¶]	NR[¶]	NR[¶]	8.31 male 11.82 female
Cheuk *et al.* 2004 [38]	East Asia	Hong Kong	0.096**	–	–	0.81**	
Vazquez *et al.* 2013 [35]	Southern Latin America	Argentina (2006–2012)	NR[¶]	NR[¶]	NR[¶]	NR[¶]	5.93
Jang *et al.* 2011 [36]	High Income Asia Pacific	Korea (2008)	0.099 male 0.097 female	0.173 male 0.131 female	0.381 male 0.412 female	0.765 male 1.042 female	1.088 male 1.092 female

Risk factors für venous thromboembolism

Strong risk factors (odds ratio > 10)

Fracture (hip or leg)

Hip or knee replacement

Major general surgery

Major trauma

Spinal cord injury

Intermediate risk factors (odds ratio 2 to 9)

Arthroscopic knee surgery

Central venous lines

Chemotherapy

Chronic heart or respiratory failure

Hormone therapy

Malignancy

Oral contraceptive therapy

Paralytic stroke

Pregnancy/postpartum

Previous venous thromboembolism

Thrombophilia

Weak risk factors (odds ratio < 2)

Bed rest longer than three days

Immobility due to sitting (e.g., car or air travel longer than eight hours)

Increasing age

Laparoscopic surgery

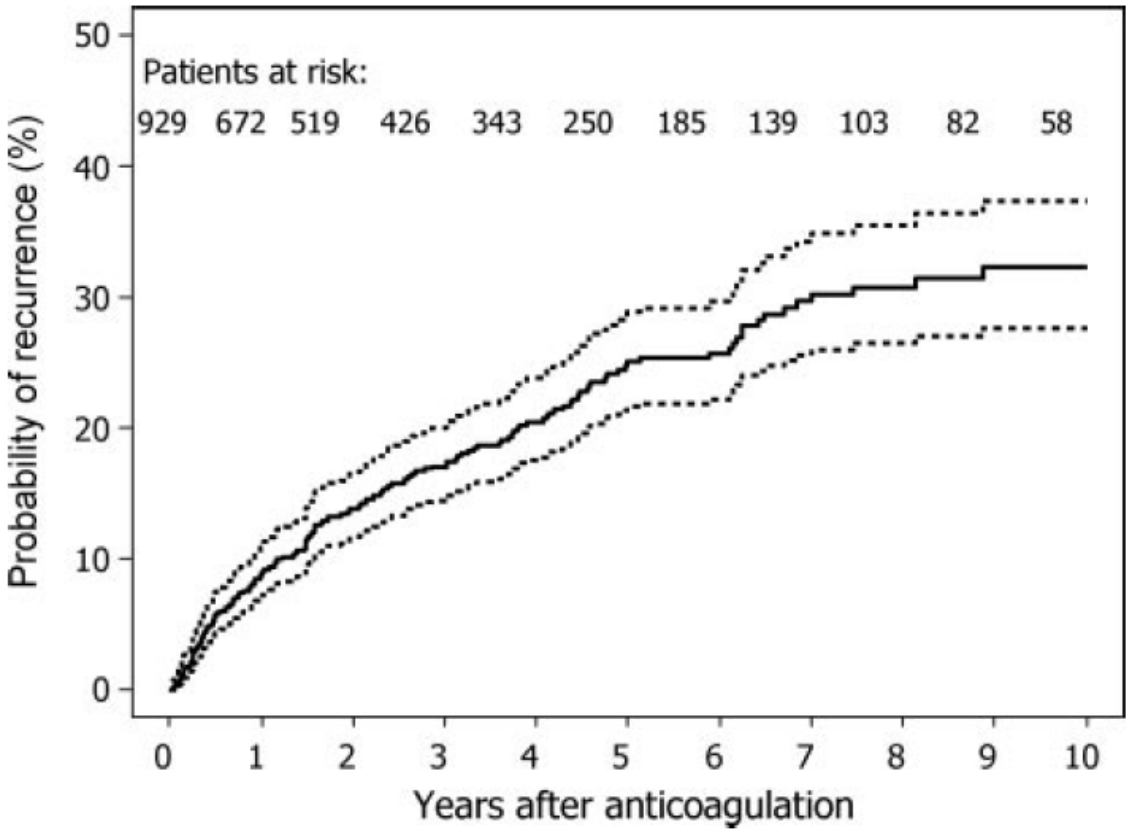
Obesity (body mass index greater than 40 kg per m^2)

Pregnancy/antepartum

Varicose veins

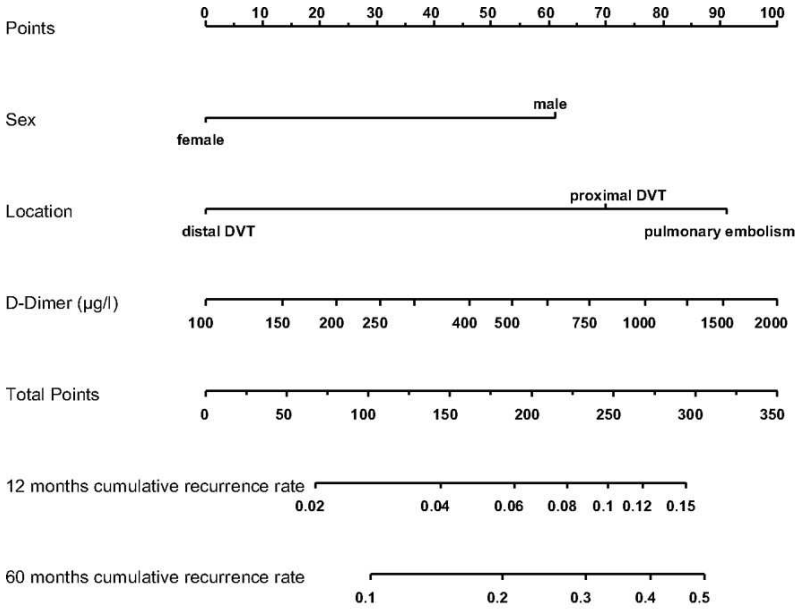
Am Fam Physician. 2012 Nov 15;86(10):913-919

Overall cumulative recurrence rate in patients with a first unprovoked VTE estimated by Kaplan-Meier analysis, with 95% CIs (dotted lines).



Circulation. 2010;121:1630-1636.

Nomogram to compute shrunken risk scores and estimate cumulative recurrence rates of recurrent VTE by use of sex, location of VTE, and D-dimer.



95% confidence intervals (CI) for cumulative recurrence rates

Time point	Recurrence Rate	95% CI
12 months	2%	1.1 - 3.7
	4%	2.6 - 6.2
	6%	4.0 - 9.0
	8%	5.7 - 11.0
	10%	7.3 - 14.0
	12%	8.4 - 17.0
	15%	9.7 - 23.0
60 months	10%	5.8 - 17
	20%	14 - 29
	30%	24 - 37
	40%	28 - 55
	50%	35 - 68

Sabine Eichinger et al. Circulation. 2010;121:1630-1636

Pulmonalarterienembolie

Inzidenz

- ca 15% aller Todesfälle im Krankenhaus
- nur 1/3 Diagnose ante mortem
- Keine Änderung der Mortalitätsrate innerhalb der letzten 25 Jahre
- ≥ 80 = 10.7% der Bevölkerung VTE

E. Pilger 2004, Thieme, ISBN-10: 3131389915

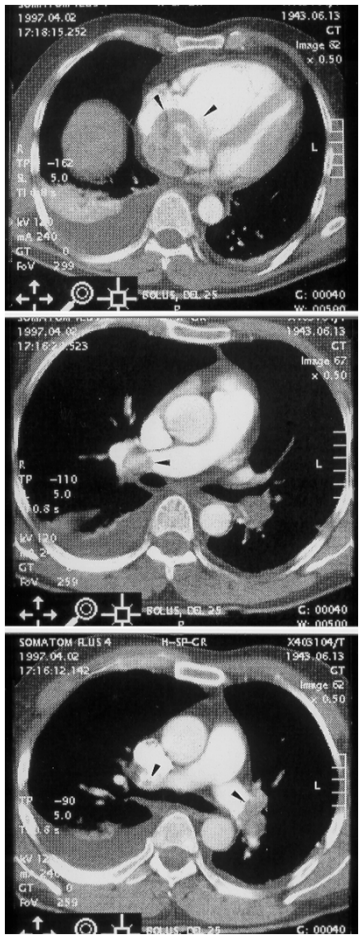
Epidemiologie u. PAE

Inzidenz der PAE :

46% wenn die TVT im Unterschenkel lokalisiert ist

67% wenn der Oberschenkel mitbetroffen ist

77% wenn die Ausdehnung bis zu den Beckenvenen reicht



E. Pilger 2004, Thieme, ISBN-10: 3131389915

Table 3. **Patient Outcomes at 3 Months after Exclusion of Pulmonary Embolism***

Diagnostic Work-up	Patients Receiving Appropriate Management (n = 418)	Patients Receiving Inappropriate Management (n = 506)	*P* Value
Total thromboembolic events, n (%)	5 (1.2)	39 (7.7)	<0.001
Nonfatal thromboembolic event, n	2	10	0.045
Unexplained sudden death, n	3	29	<0.001

* Patients who received anticoagulation for reasons other than thromboembolic disease were excluded from follow-up analysis.

Ann Intern Med. 2006;144:157-164

Diagnostik

Clinical Model for Predicting Pretest Probability for Deep-Vein Thrombosis

Clinical feature	*Score*
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden longer than 3 days or major surgery, within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or greater than that of deep-vein thrombosis	–2

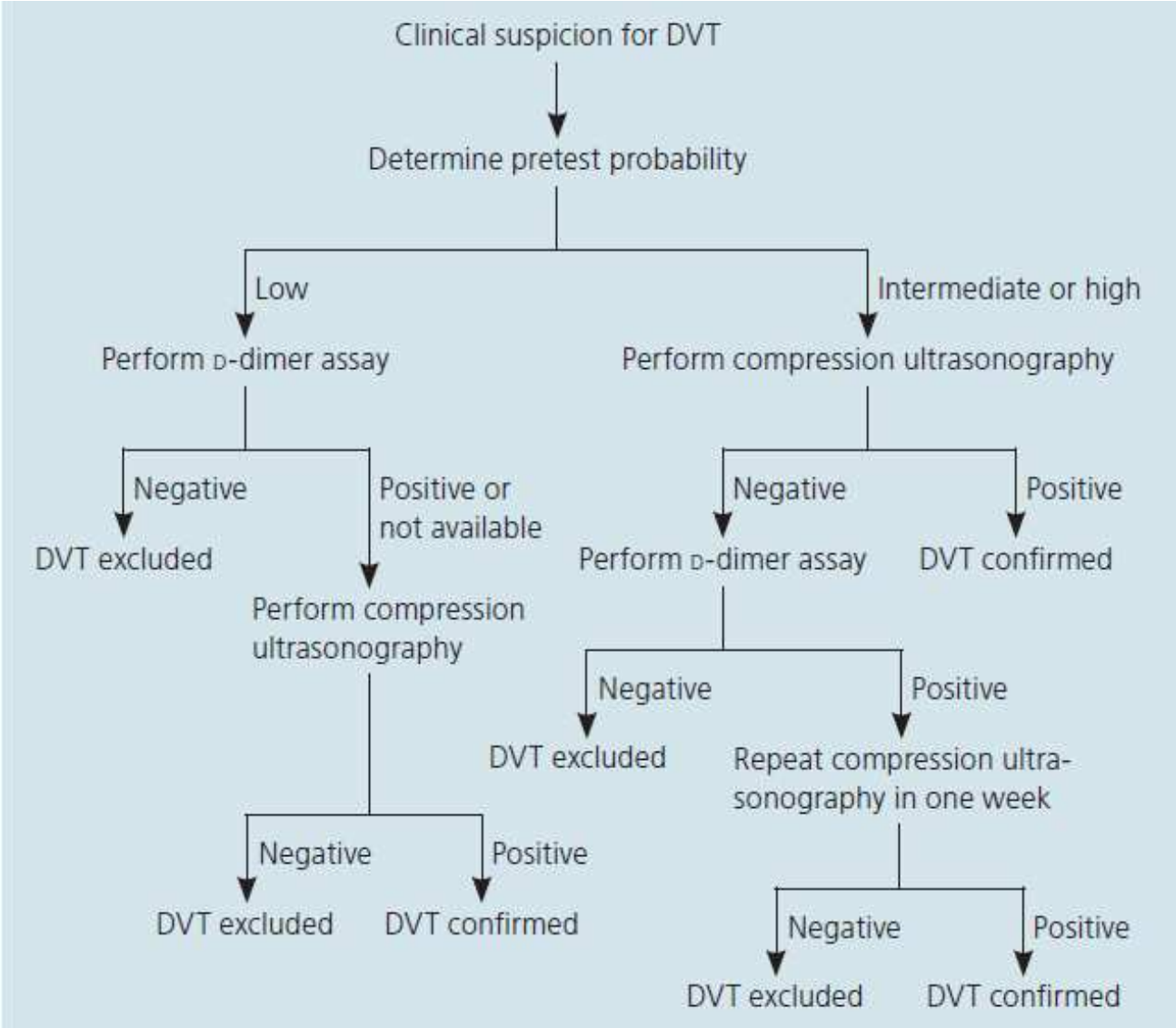
Clinical pretest probability	*Total*
Low	≤ 0
Intermediate	1 or 2
High	≥ 3

NOTE: *In patients with symptoms in both legs, the more symptomatic leg is used.*

Reprinted with permission from Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet. *1997;350(9094):1796.*

Am Fam Physician. 2012 Nov 15;86(10):913-919

Algorithm for the diagnosis of deep venous thrombosis (DVT)



Am Fam Physician. 2012 Nov 15;86(10):913-919

Clinical characteristics of patients with suspected PE in the emergency department (adapted from Pollack et al. (2011))

Feature	PE confirmed (*n* = 1880)	PE not confirmed (*n* = 528)
Dyspnoea	50%	51%
Pleuritic chest pain	39%	28%
Cough	23%	23%
Substernal chest pain	15%	17%
Fever	10%	10%
Haemoptysis	8%	4%
Syncope	6%	6%
Unilateral leg pain	6%	5%
Signs of DVT (unilateral extremity swelling)	24%	18%

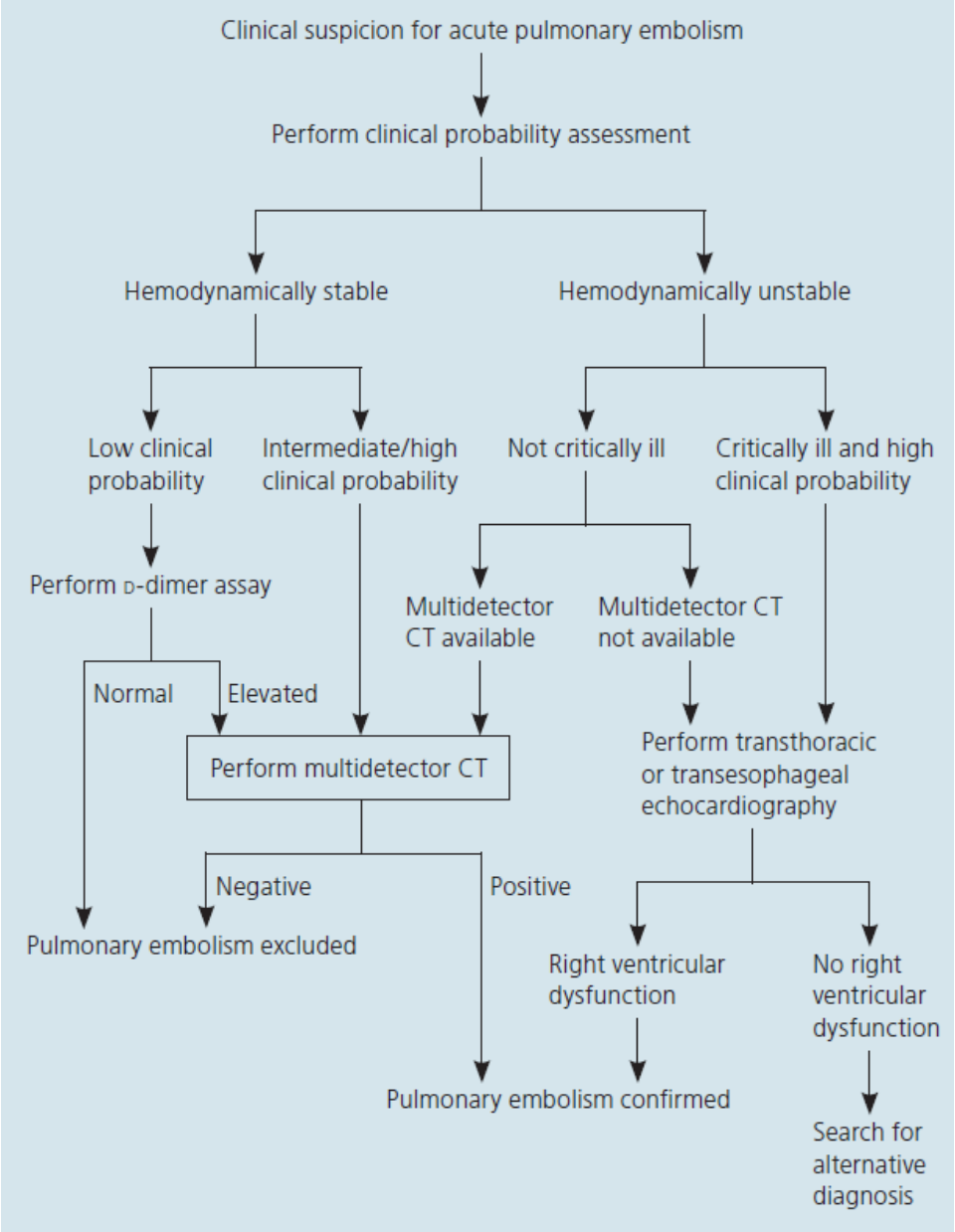
European Heart Journal (2014) 35, 3033–3080

Clinical Rule for Predicting Pretest Probability for Pulmonary Embolism

Clinical feature	*Score*
Alternative diagnosis less likely than pulmonary embolism	3
Clinical signs and symptoms of deep venous thrombosis	3
Heart rate greater than 100 beats per minute	1.5
Previous pulmonary embolism or deep venous thrombosis	1.5
Recent surgery (in the previous four weeks) or immobilization (in the previous four days)	1.5
Cancer	1
Hemoptysis	1
Clinical pretest probability	*Total*
Low	< 2
Intermediate	2 to 6
High	≥ 7

Adapted with permission from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. *2000;83(3):418.*

Algorithm for the diagnosis of pulmonary embolism



Am Fam Physician. 2012 Nov 15;86(10):913-919

Untersuchungsergebnisse bei PAE

Ventilations u. Perfusionsscintigraphie:

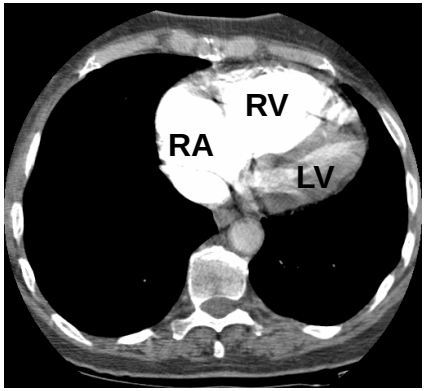
•Sensitivität	92 %
•Pos. Präd. Faktor	92 %
•Intra- inter observer variability	10 - 20 %

Echokardiographie:

- •LV/RV > 0,5
- •V_{Reg} über Tricuspidalklappe > 2,5 m/s

Sensitivität f. PAE = 93 %

Spezifität f. PAE = 81 %

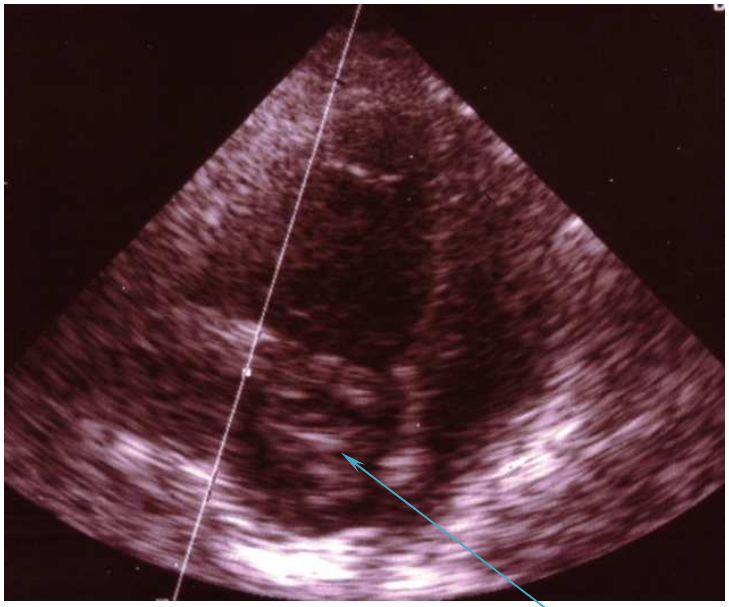


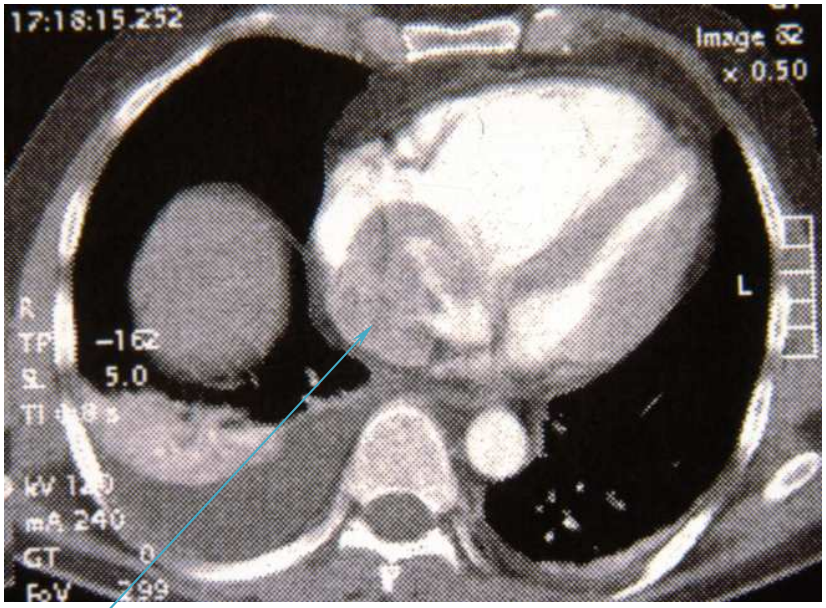
D-Dimer (ELISA):

- •> 500 µg/l
- •Sensitivität = 99 % (Ausschluß einer PAE)

E. Pilger 2004, Thieme, ISBN-10: 3131389915

Pulmonary embolism and intracardiac thrombus

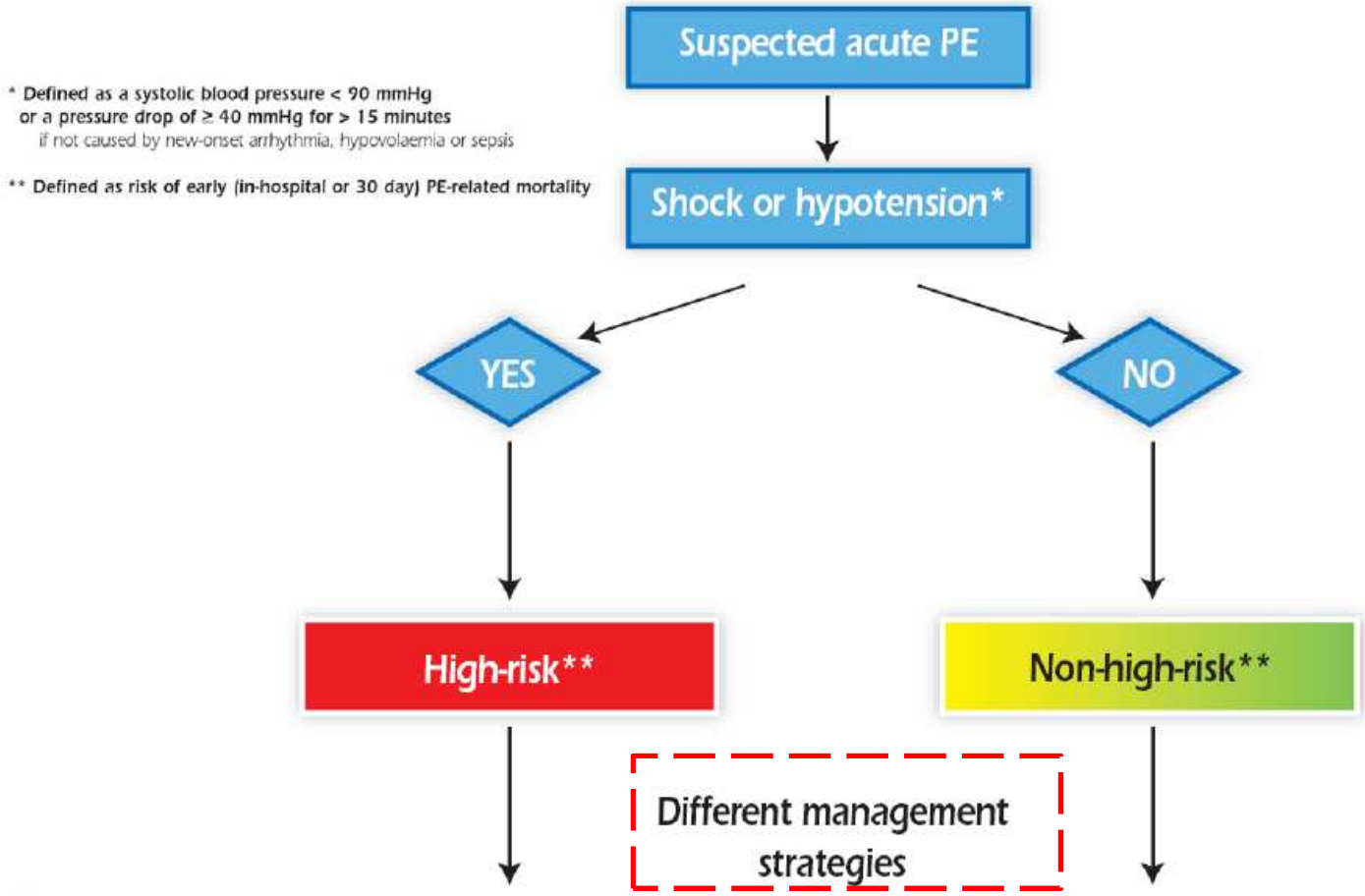




Thrombus in the right atrium

Therapie

Initial Risk Stratification



European Heart Journal (2014) 35, 3033–3080

Pulmonalarterienembolie

Risikoabschätzung

Prinzipielle Marker sinnvoll in der Risikoabschätzung“

Clinical markers	Shock
	Hypotension[a]
Markers of RV dysfunction	RV dilatation, hypokinesis or pressure overload on echocardiography
	RV dilatation on spiral computed tomography
	BNP or NT-proBNP elevation
	Elevated right heart pressure at RHC
Markers of myocardial injury	Cardiac troponin T or I positive[b]

a) ist definiert als systolischer RR <90 mmHG oder Abfall des systolischen RR >40 mmHG in 15 Minuten nicht verursacht durch neuaufgetretene Arrythmie, Sepsis oder Hypovolämie

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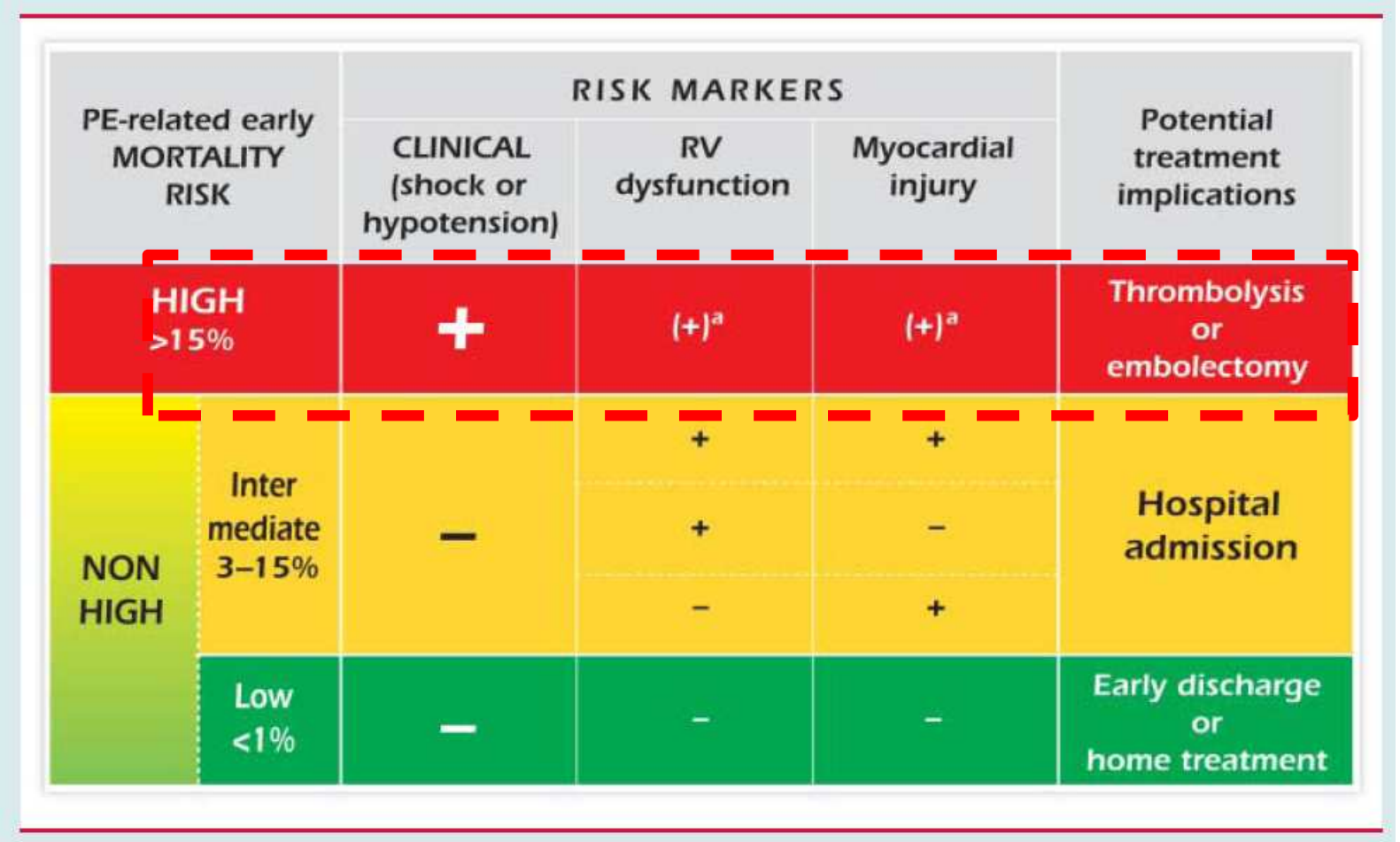
Risikoabschätzung Mortalität



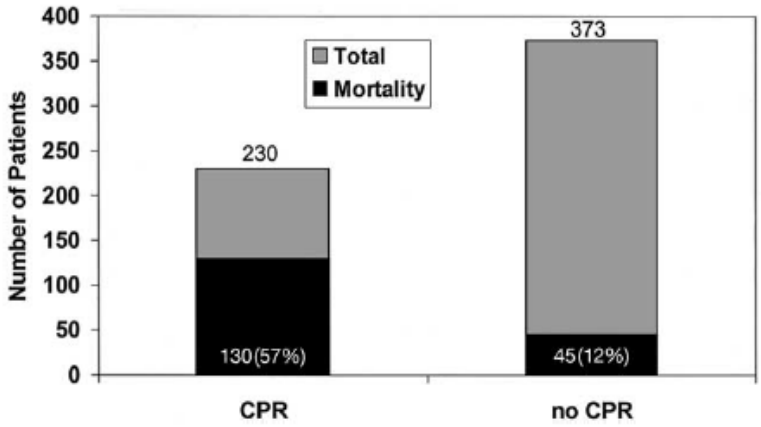
PE-related early MORTALITY RISK		RISK MARKERS			Potential treatment implications
		CLINICAL (shock or hypotension)	RV dysfunction	Myocardial injury	
HIGH >15%		+	(+)[a]	(+)[a]	Thrombolysis or embolectomy
NON HIGH	Inter mediate 3–15%	–	+	+	Hospital admission
			+	–	
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment

European Heart Journal (2014) 35, 3033–3080

High Risk

Chirurgische Embolektomie

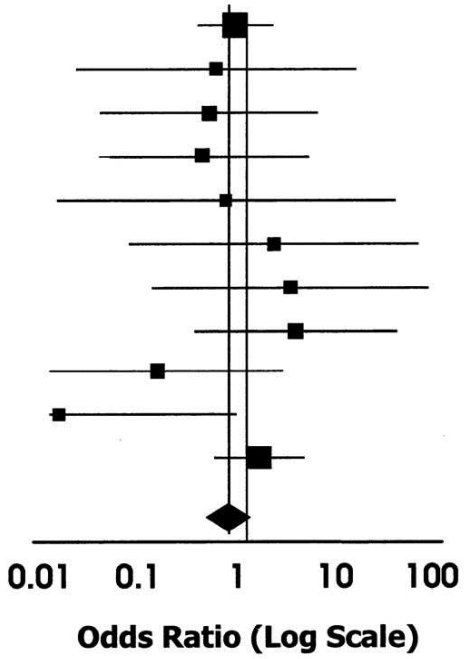
Year	Author	Total	Deaths	Mortality %
1978	Tschirkov (Germany)	24	7	29
1981	Clark (England)	42	23	55
1981	Glassford (England)	20	8	40
1981	Bottzauw (Denmark)	23	6	26
1982	Mattox (US)	40	20	50
1985	Achatzy (Germany)	10	4	40
1986	Jaumin (France)	23	7	30
1988	Gray (England)	71	21	30
1990	Meyer (France)	96	36	38
1991	Boulafendis (US)	16	5	31
1991	Kieny (France)	134	21	16
1991	Schmid (Germany)	27	12	44
1991	Bauer (Switzerland)	44	11	25
1992	Meyns (Belgium)	30	6	20
1994	Stutz (Switzerland)	50	23	46
1995	Jakob (Germany)	25	6	24
1999	Doerge (Germany)	41	12	29
1999	Ullmann (Germany)	40	14	35
	Total	756	242	32



Ann Thorac Surg; 2005:79:1240

Recurrent pulmonary embolism or death in trials comparing thrombolysis with heparin for initial treatment of acute pulmonary embolism.

Study	Thrombolysis	Heparin	OR	95% CI
UPET, 1973	10/82	14/78	0.63	0.26 - 1.53
Tibbutt et al, 1974	0/13	1/17	0.41	0.02 - 10.83
Ly et al, 1978	1/14	2/11	0.35	0.03 - 4.42
Dotter et al, 1979	1/15	3/16	0.31	0.03 - 3.36
Marini et al, 1988	0/20	0/10	0.51	0.01 - 27.68
PIOPED, 1990	1/9	0/4	1.59	0.05 - 47.52
Levine et al, 1990	1/33	0/25	2.35	0.09 - 60.24
Dalla-Volta et al, 1992	3/20	1/16	2.65	0.25 - 28.24
Goldhaber et al, 1993	0/46	4/55	0.12	0.01 - 2.35
Jerjes-Sanchez et al, 1995	0/4	4/4	0.01	0.00 - 0.77
Konstantinides et al, 2002	8/118	7/138	1.36	0.48 - 3.87
Total	**25/374**	**36/374**	**0.67**	**0.40 - 1.12**

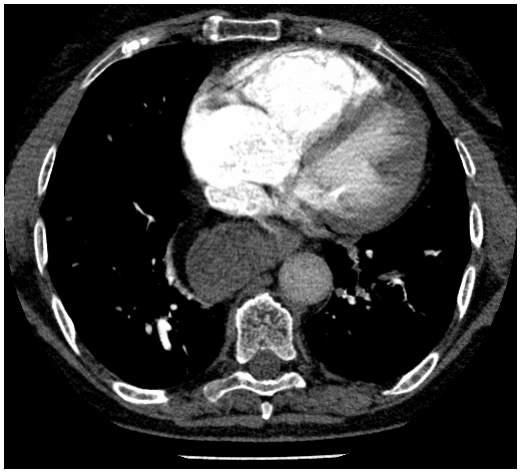


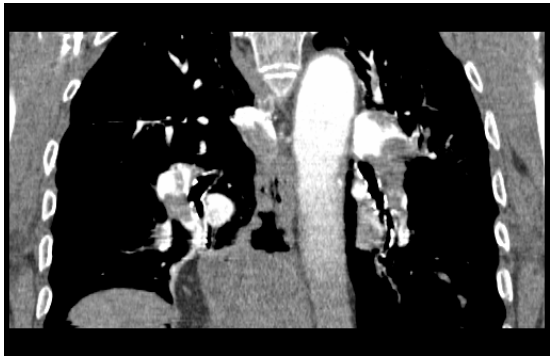
Circulation. 2004;110:744-749

PAE

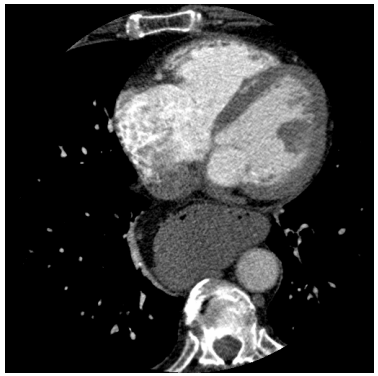
Pat.: 74 a
Symptomatik seit 3 die mit Progred.
Pat kann wenige Schritte ohne Dyspnoe gehen

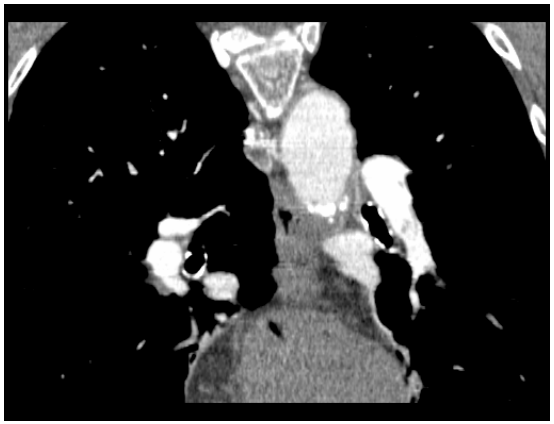
Vor fibrinolytischer Therapie



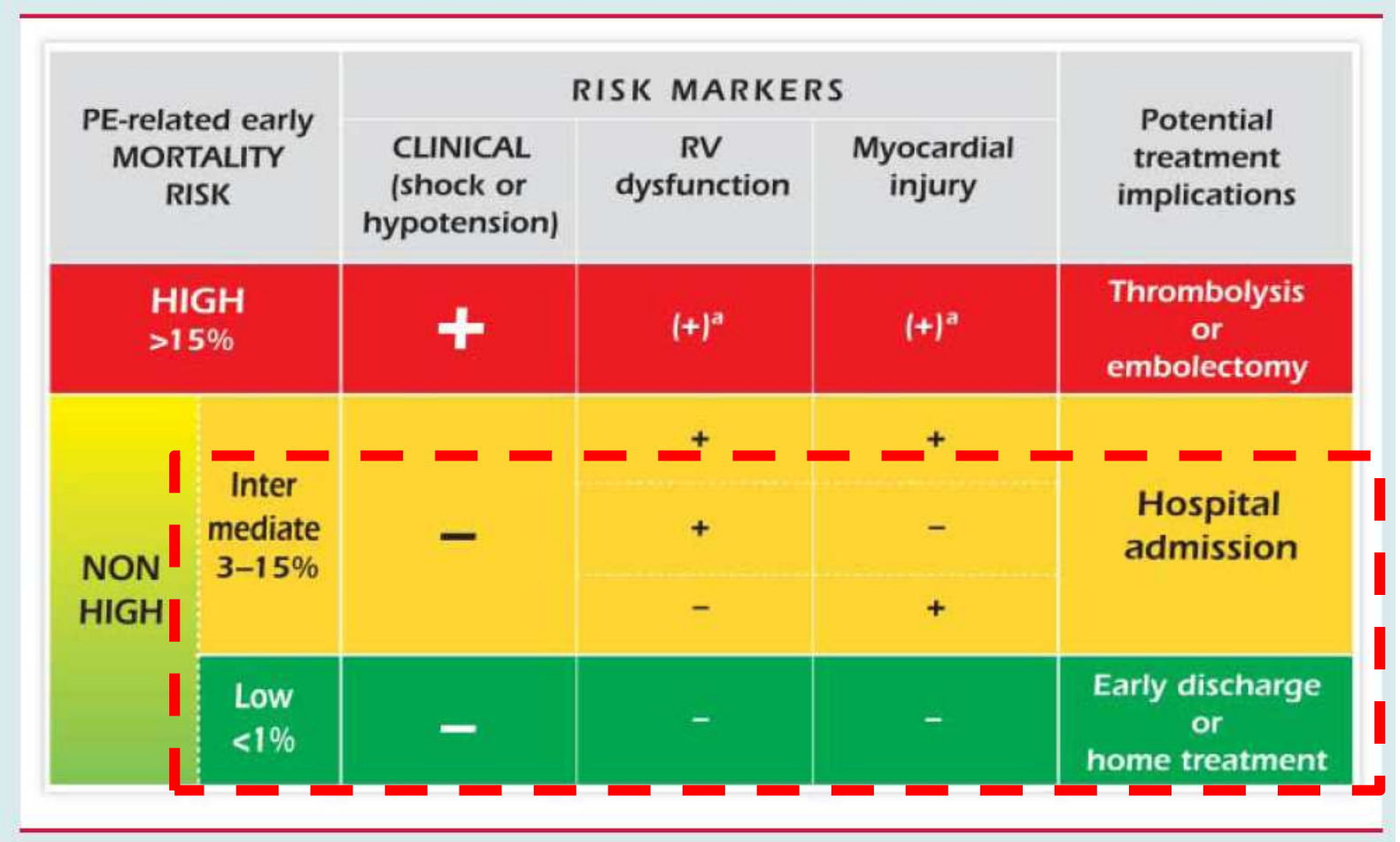


Nach fibrinolytischer Therapie mit
70 mg rtPa / 2 h





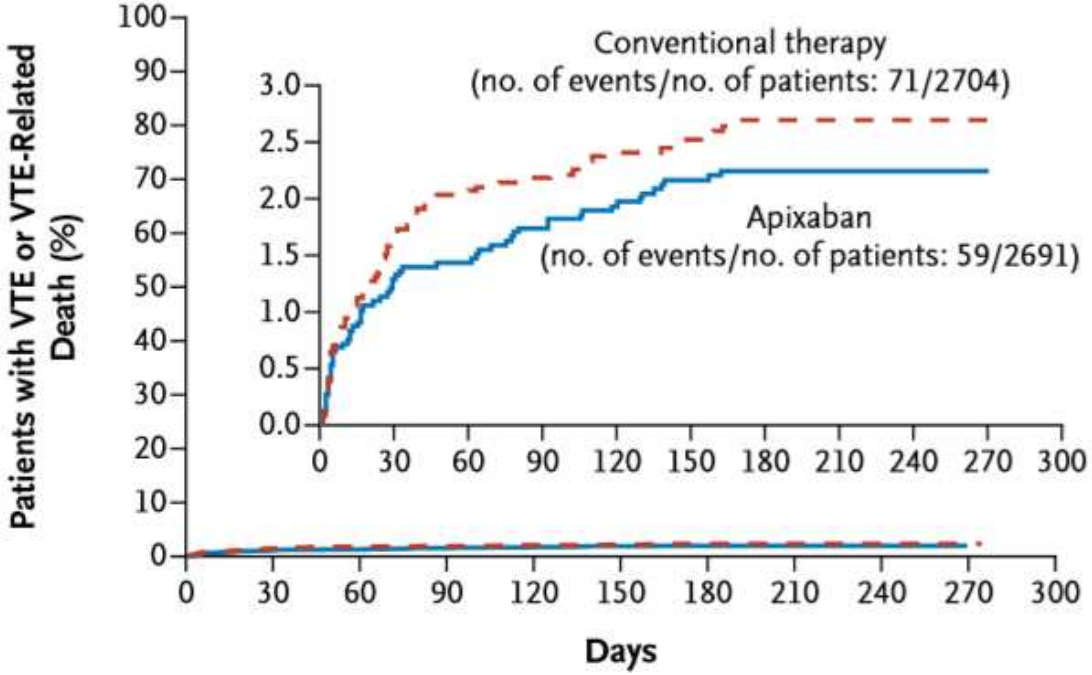
Risikoabschätzung Mortalität



PE-related early MORTALITY RISK		RISK MARKERS			Potential treatment implications
		CLINICAL (shock or hypotension)	RV dysfunction	Myocardial injury	
HIGH >15%		+	(+)[a]	(+)[a]	Thrombolysis or embolectomy
NON HIGH	Intermediate 3–15%	–	+	+	Hospital admission
			+	–	
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment

European Heart Journal (2014) 35, 3033–3080

Oral Apixaban for the Treatment of Acute Venous Thromboembolism

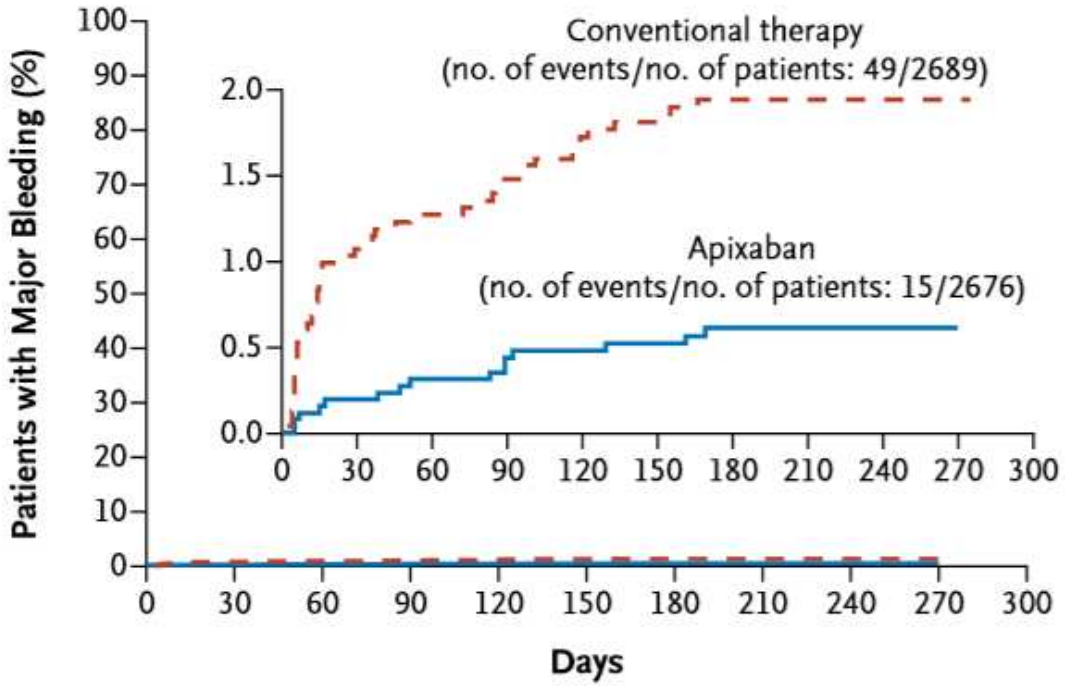


No. at Risk

Apixaban	2691	2606	2586	2563	2541	2523	62	4	1	0	0
Conventional therapy	2704	2609	2585	2555	2543	2533	43	3	1	1	0

N Engl J Med 2013;369:799-808

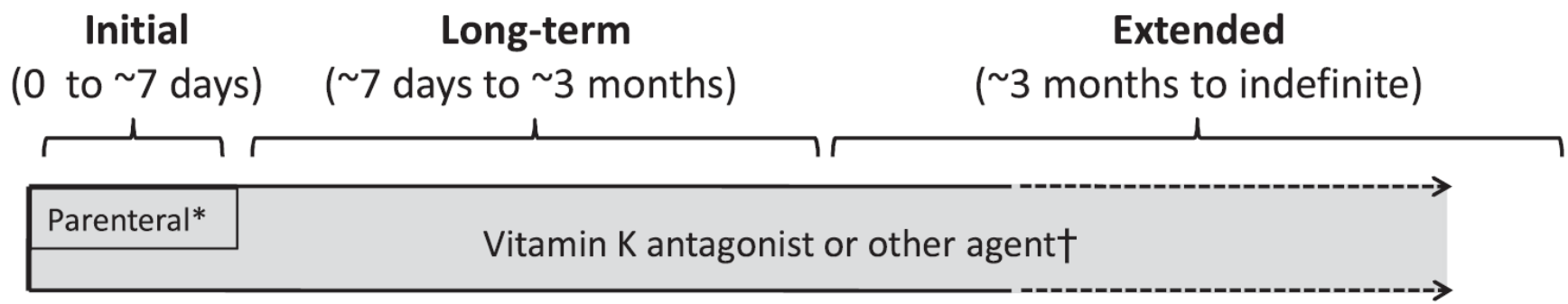
Oral Apixaban for the Treatment of Acute Venous Thromboembolism



No. at Risk											
Apixaban	2676	2519	2460	2409	2373	2339	61	4	1	0	0
Conventional therapy	2689	2488	2426	2383	2339	2310	43	3	1	1	0

N Engl J Med 2013;369:799-808

Phases of anticoagulation



* Heparin, LMWH, fondaparinux ; † Includes LMWH, dabigatran, rivaroxaban

Design and patient characteristics of the trials comparing NOAC with conventional therapy for acute VTE treatment

	Dabigatran	Rivaroxaban		Apixaban	Edoxaban
Trial	RE-COVER I & II	EINSTEIN		AMPLIFY	Hokusai-VTE
Indication	VTE	DVT	PE	VTE	VTE
Design	Double-blind	PROBE		Double-blind	Double-blind
Number of patients	2539 2568	3449	4832	5365	8240
Mean age ± SD (y)	54.9 ± 16.0	56.1 ± 16.4	57.7 ± 7.3	57.0 ± 16.0	55.8 ± 16.3
CrCl <30 mL/min, n (%)	22 (0.4)	15 (0.4)	6 (0.1)	29 (0.5)	n/a
Age ≥75 y, n (%)	529 (10)	440 (13)	843 (17)	768 (14)	1104 (13)
Prior VTE (%)	22	19	20	16	18
Unprovoked VTE (%)	35	62.0	64.5	89.8	65.7
Index event PE ± DVT (%)	31	0.7	100	34	40
Noninferiority margin	2.75	2.0		1.8	1.5
Bridge with heparin/LMWH	Yes	No		No	Yes
Treatment protocol	150 mg BID	15 mg BID for 3 wk; then 20 mg OD		10 mg BID for 7 d; then 5 mg BID	60 mg OD; 30 mg OD for those with a creatinine clearance of 30-50 mL/min, weight <60 kg, or taking potent P-gp inhibitors
Duration (mo)	6	3, 6, 12		6	3-12
TTR (%)	60	58	63	61	64

n/a, not available; OD, once daily; BID, twice daily; P-gp, P-glycoprotein; LMWH, low-molecular-weight heparin; PROBE, prospective, randomized, open-label, blinded endpoint; TTR, time in therapeutic range with warfarin.

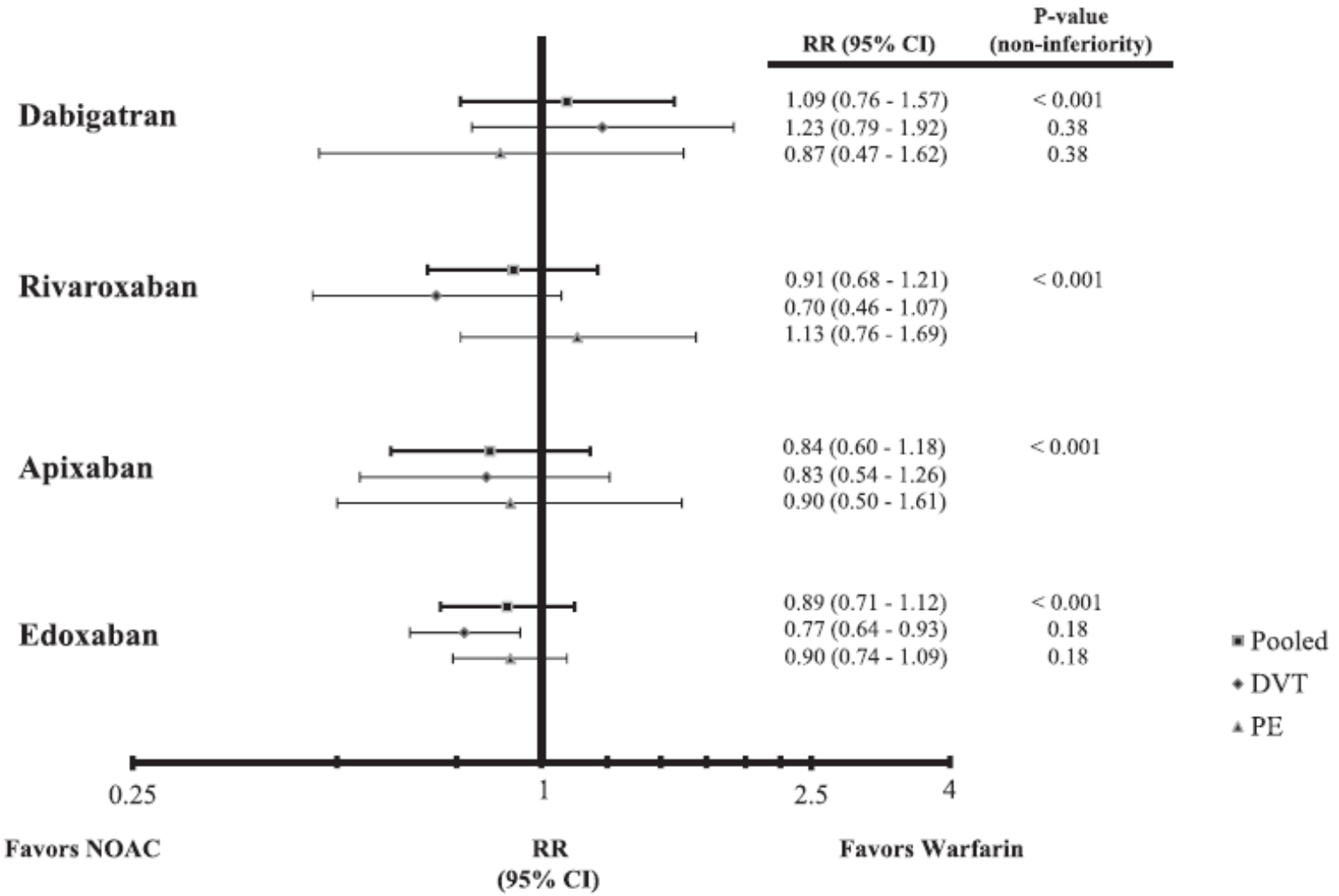
BLOOD, 14 AUGUST 2014 x VOLUME 124

Guidelines for Duration of Anticoagulant Therapy for VTE

Risk Factor for VTE	Duration of Treatment (Target INR 2.5, Range 2.0–3.0)
Transient risk factor	**3 mo**
Unprovoked (bleeding risk is low or moderate)	**Extended therapy**
If unprovoked and : high risk of bleeding	**3 mo**
Uncontrolled malignancy	**Extended therapy**

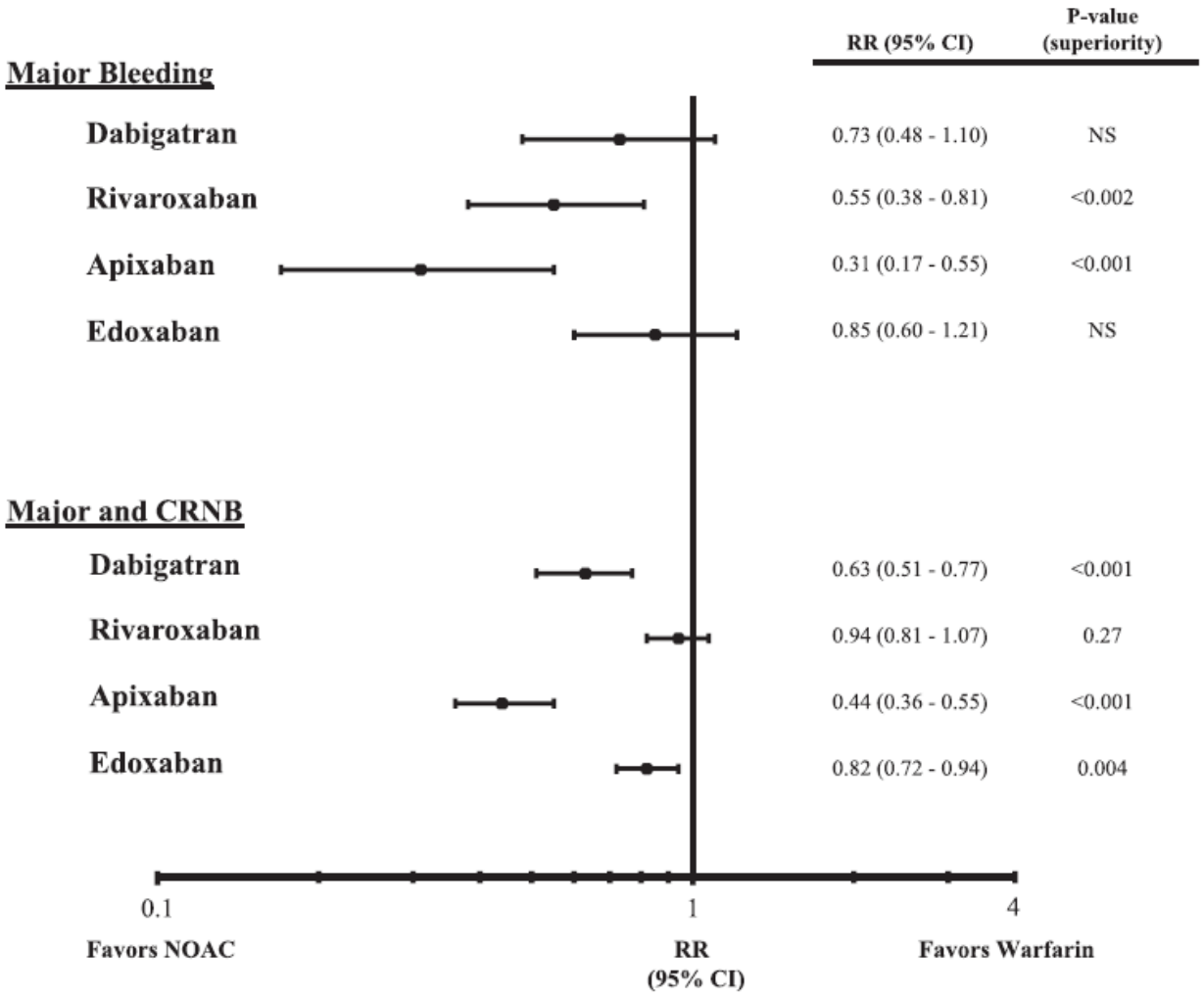
CHEST 2012

Hazard ratios (HR) for recurrent VTE and VTE-related death and their 95% confidence intervals (CI)



BLOOD, 14 AUGUST 2014 x VOLUME 124

Hazard ratios (HR) for major bleeding or major plus clinically relevant nonmajor bleeding (CRNB) and their 95% confidence intervals (CI)



Suggestions for choice of anticoagulant for acute VTE treatment

Characteristic	Drug choice	Rationale
Extensive DVT or massive PE	Heparin	Such patients often require advanced therapy and were excluded from trials with the NOACs
High initial risk of bleeding	Heparin	Enables dose titration; rapid offset and availability of protamine as an antidote simplify management should bleeding occur
Active cancer	LMWH	No trials comparing NOACs with LMWH
Pregnancy	LMWH	Warfarin and NOACs cross the placenta
Liver dysfunction with increased prothrombin time/ INR at baseline	Warfarin	Such patients were excluded from the trials because NOACs undergo hepatic metabolism
Unable to afford NOACs	LMWH followed by warfarin	NOACs cost less than LMWH but are more expensive than warfarin
Limited access to anticoagulation clinic because of impaired mobility or geographical inaccessibility	NOAC	Given in fixed doses without monitoring
All-oral therapy	Rivaroxaban or apixaban	Only NOACs to be evaluated in all-oral regimens
Creatinine clearance <30 mL/min	Warfarin	Such patients were excluded from trials with NOACs
Creatinine clearance 30-50 mL/min	Rivaroxaban, apixaban, or edoxaban	Less affected by renal impairment than dabigatran; if edoxaban is chosen, the 30-mg OD dose should be used
Dyspepsia or upper gastrointestinal symptoms	Rivaroxaban, apixaban, or edoxaban	Dyspepsia in as much as 10% given dabigatran
Recent gastrointestinal bleed	Apixaban	More gastrointestinal bleeding with dabigatran, rivaroxaban, and edoxaban than with warfarin
Recent acute coronary syndrome	Rivaroxaban, apixaban or edoxaban	Small myocardial infarction signal with dabigatran
Poor compliance with long-term twice-daily dosing	Rivaroxaban or edoxaban	OD regimens for long-term use

OD, once daily; LMWH, low-molecular-weight heparin.

Zusammenfassung I:

- Das Erkennen einer VTE ist ausschlaggebend für die Prognose.

- Die Vortestwahrscheinlichkeit entscheidet über das diagnostische Vorgehen bei einer VTE.

- Die Risikoeinschätzung bez. der Mortalität entscheidet über das Therapeutische Vorgehen.

- Die Langzeittherapie (AK betreffend) ist bei einer VTE der einer DVT gleichzusetzen.

Zusammenfassung II:

- Die neuen oralen Antikoagulantien (NOAK) ermöglichen eine den Vitamin-K-Antagonisten ebenbürtige Antikoagulation bei geringerem Risiko für intrakranielle Blutungen.

- Bei Therapie mit NOAK ist keine routinemässige Kontrolle der gerinnungshemmenden Wirkung nötig.

- Die Grenzen der Anwendung sind unbedingt einzuhalten, speziell bei Niereninsuffizienz oder Leberinsuffizienz.

FASZINATION

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