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NAPOLI 17-20 NOVEMBRE 2016

Embolia polmonare a “basso rischio” siamo pronti per la gestione domiciliare?

Simone Vanni, MD, PhD

Centro di riferimento regionale toscano per la diagnosi ed il trattamento della Embolia Polmonare acuta

DEA- Azienda Ospedaliero-Universitaria Careggi

Embolia Polmonare

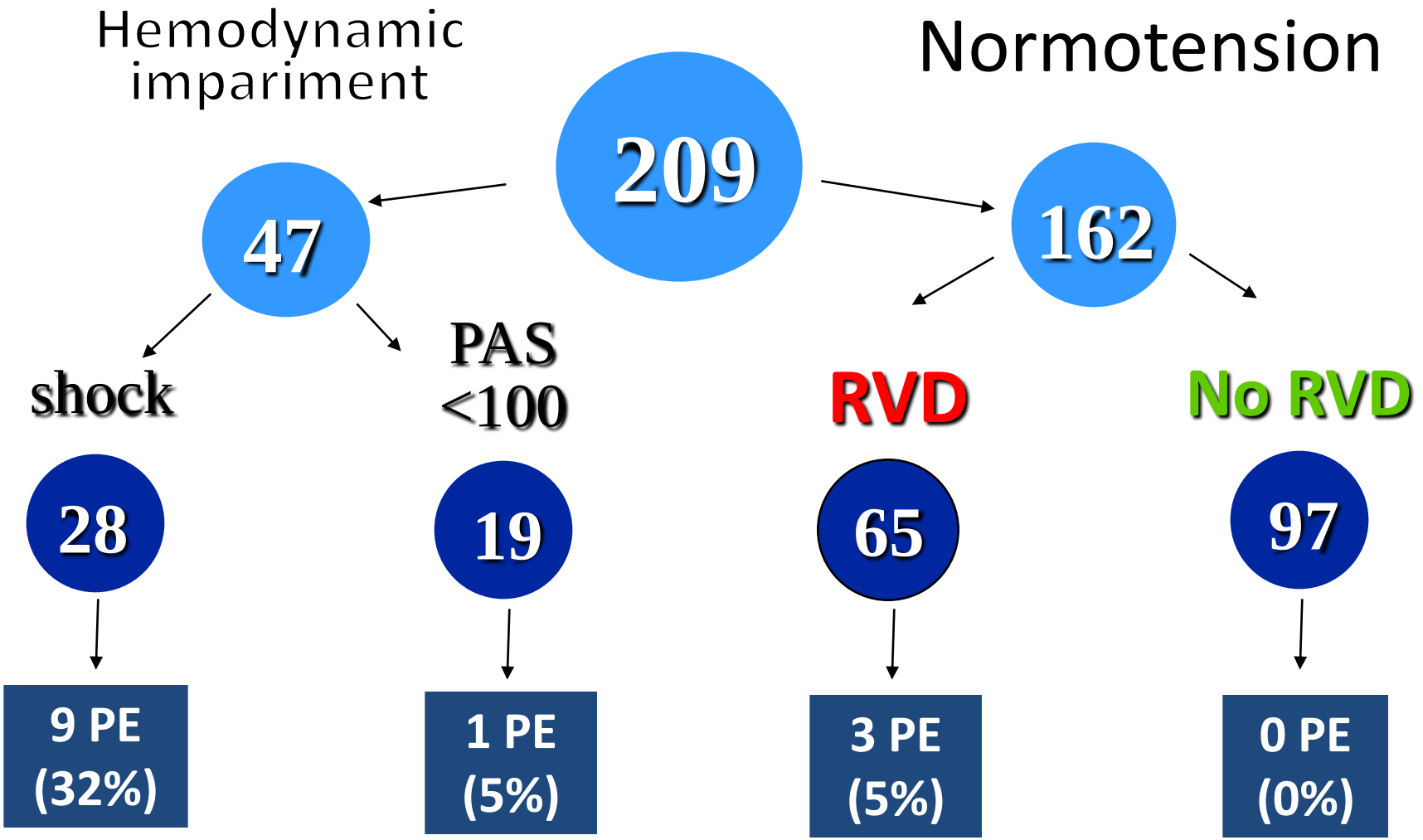
"Pulmonary embolism afflict millions of individuals worldwide and account for several hundred thousand deaths annually...

Few healthcare providers realize that the fatality rate for PE , approximately 15 percent, exceeds the mortality rate for acute myocardial infarction..."

Samuel Z. Goldhaber. Professor of Medicine at Harvard Medical School

Braunwald's Heart Disease, 8° edition, 2008

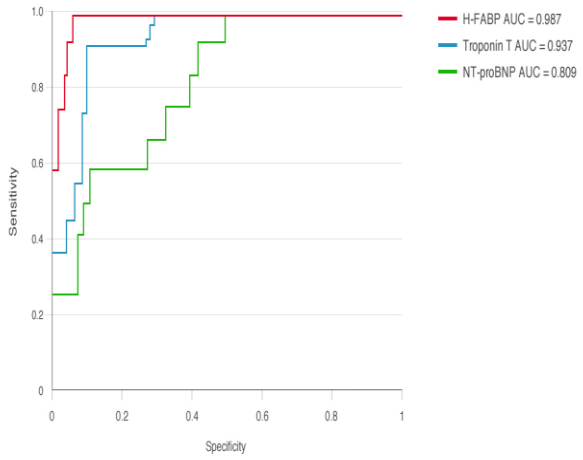
RVD and normotensive patients

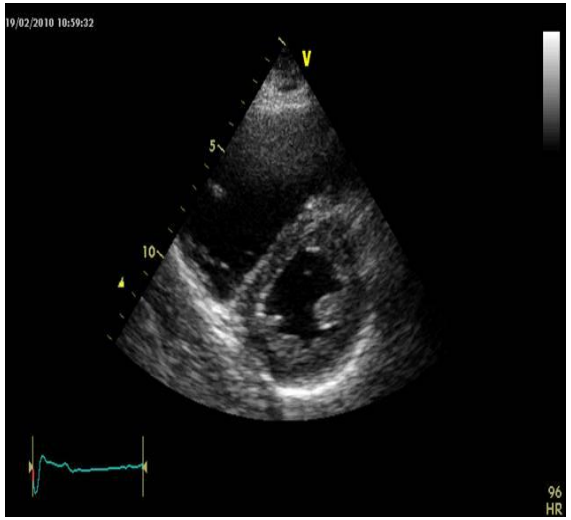


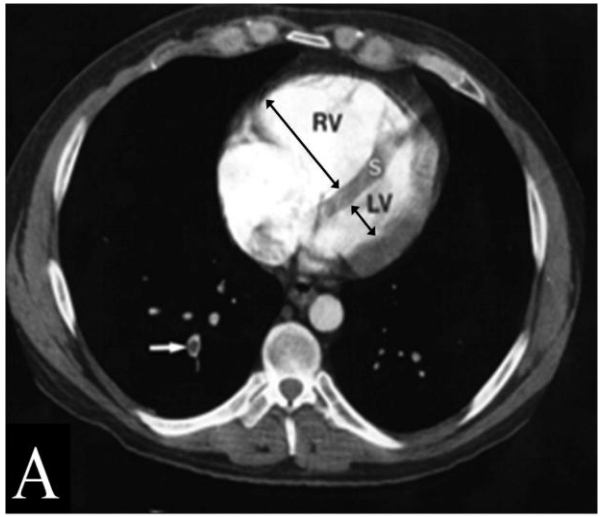
Grifoni et al. Circulation 2000

La prognosi del paziente con Embolia Polmonare

- Chi sono i pazienti a basso rischio?
- Quanti sono?
- Quale trattamento?







Classification of patients with Pulmonary Embolism based on early mortality risk

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

ESC Guidelines 2008

PESI vs sPESI

Table 1. Original and Simplified Pulmonary Embolism Severity Index (PESI)

Variable	Score: Original PESI[a]	Score: Simplified PESI[b]
Age >80 y	Age in years	1
Male sex	+10	
History of cancer	+30	1
History of heart failure	+10	1[c]
History of chronic lung disease	+10	
Pulse ≥110 beats/min	+20	1
Systolic blood pressure <100 mm Hg	+30	1
Respiratory rate ≥30 breaths/min	+20	
Temperature <36°C	+20	
Altered mental status	+60	
Arterial oxyhemoglobin saturation level <90%	+20	1

Jimenez et al, Arch Intern med 2010

Quanti sono i pazienti basso rischio?

Table 3 Distribution of patients and adverse events within risk strata derived from the Pulmonary Embolism Severity Index (PESI) and the European Society of Cardiology (ESC) models

	Patients, *n* (%, 95% CI)	Death, *n* (%, 95% CI)	PE death, *n* (%, 95% CI)	Secondary outcomes, *n* (%, 95% CI)
ESC				
Low	194 (40, 36–45)*	5 (2, 1–6)	2 (1, 0–4)	6 (3, 1–7)
Intermediate	264 (54, 50–59)	24 (9, 6–13)	17 (6, 4–10)	19 (7, 5–11)
High	27 (6, 4–8)*	8 (30, 16–49)	8 (30, 16–49)	6 (22, 10–41)
PESI				
Low	145 (31, 28–36)	4 (3, 1–7)	1 (1, 0–4)	3 (2, 0–6)
Intermediate	226 (49, 44–54)	14 (6, 3–10)	10 (4, 2–8)	15 (7, 4–11)
High	92 (20, 16–24)	20 (22, 14–32)	14 (15, 9–24)	14 (15, 9–24)

CI, confidence interval; PE, pulmonary embolism. The total numbers of patients available for the analysis were 485 for the ESC model (4.9% missing) and 463 for the PESI model (9.2% missing). Secondary outcomes: non-fatal PE recurrences, delayed hemodynamic instability or non-fatal major bleeding during in-hospital stay. *$P < 0.05$ vs. PESI model.

Quanti sono i pazienti a basso rischio

Table 3. Thirty-Day Mortality Within Risk Strata Derived From the Original and the Simplified PESI in the Derivation and Validation Cohorts

PESI Risk Categories	Original PESI Derivation Cohort, % (95% CI)		Simplified PESI Derivation Study Cohort, % (95% CI)		Simplified PESI Validation (RIETE) Cohort, % (95% CI)	
	Patients (n=10 354)	Deaths[a] (n=953)	Patients (n=995)	Deaths (n=78)	Patients (n=7106)	Deaths (n=434)
Original						
I	19.4 (18.7-20.2)	1.1 (0.7-1.7)	14.3 (12.1-16.4)[b]	2.1 (0.2-4.5)		
II	21.5 (20.7-22.3)	3.1 (2.5-4.0)	22.0 (19.4-24.6)	2.7 (0.6-4.9)		
III	21.7 (20.9-22.5)	6.5 (5.5-7.6)	27.7 (25.0-30.5)[b]	5.4 (2.8-8.1)		
IV	16.4 (15.7-17.1)	10.4 (9.0-11.9)	21.5 (18.9-24.1)[b]	10.3 (6.2-14.3)		
V	21.0 (20.3-21.8)	24.5 (22.7-26.9)	14.5 (12.3-16.7)[b]	22.2 (15.4-29.0)		
Low[d]	40.9 (40.0-41.8)	2.1 (1.7-2.6)	36.3 (33.3-39.3)[c]	2.5 (0.9-4.1)		
High[d]	59.1 (58.1-60.0)	14.0 (13.1-14.9)	63.7 (60.7-66.7)	10.9 (8.5-13.3)		
Simplified						
Low			30.7 (27.8-33.5)	1.0 (0.0-2.1)	36.1 (35.0-37.3)[e]	1.1 (0.7-1.5)
High			69.3 (66.5-72.2)	10.9 (8.5-13.2)	63.9 (62.7-65.0)	8.9 (8.1-9.8)

Abbreviations: CI, confidence interval; PESI, Pulmonary Embolism Severity Index; RIETE, Registro Informatizado de la Enfermedad Tromboembólica.
[a] Per risk stratum.
[b] For comparison between the original and the simplified PESI derivation samples, $P<.001$.
[c] For comparison between the original and the simplified PESI derivation samples, $P<.01$.
[d] Original PESI class I and II categories are classified as low risk, and classes III through V are classified as high risk.
[e] For comparison between the simplified PESI derivation sample and the simplified PESI validation sample, $P<.001$.

Arch Intern Med. 2010;170(15):1383-1389

Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial

Drahomir Aujesky, Pierre-Marie Roy, Franck Verschuren, Marc Righini, Joseph Osterwalder, Michael Egloff, Bertrand Renaud, Peter Verhamme, Roslyn A Stone, Catherine Legall, Olivier Sanchez, Nathan A Pugh, Alfred N'gako, Jacques Cornuz, Olivier Hugli, Hans-Jürg Beer, Arnaud Perrier, Michael J Fine, Donald M Yealy

	Outpatient group	Inpatient group	Difference in percentages ($\%_{outpatient} - \%_{inpatient}$)	Upper 95% CL for difference	p value*
Primary analysis outcomes within 90 days†					
Recurrent VTE	1 (0·6%)‡	0	0·6%	2·7%	0·011
Major bleeding	3 (1·8%)	0	1·8%	4·5%	0·086
Intramuscular	2 (1·2%)	0	1·2%	3·6%	0·031
Menometrorrhagia	1 (0·6%)	0	0·6%	2·7%	0·011
Overall mortality	1 (0·6%)§	1 (0·6%)¶	0%	2·1%	0·005

Interpretation In selected low-risk patients with pulmonary embolism, outpatient care can safely and effectively be used in place of inpatient care.

Lancet 2011

Studi clinici basso rischio

Study	Type	No	Excluded	Recurrent VTE	Major Haemorr
Otero et al (Thrombosis Research 2008)	RCT-multicenter	132	884	3% (0.75%)	1.5% (0.75%)
Erkens et al (J Thromb Haemost 2010)	Retrospective	260	245	3.6% (0)	1.5% (0)
Agterof et al (J Thromb Haemost 2010)	Prospective multicenter	152	199	1.9% (0)	0
Zondag et al (J Thromb Haemost 2011)	Prospective observational	297	243	2% (0)	0.8% (0)
Aujesky et al (Lancet 2011)	RCT-multicenter	344	1148	0.6% (0)	1.8% (0)

1185 patients, 23 recurrent VTE (1.9%), 11 major bleeds (0.9%)

Basso rischio definizione ESC

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

ESC Guidelines 2008

Basso rischio definizione ESC

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III–V or sPESI ≥I[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate–high	-	+	Both positive	
	Intermediate–low	-	+	Either one (or none) positive[e]	
Low		-	-	Assessment optional; if assessed, both negative[e]	

RV/biomarkers assessment optional
if assessed both negative

Konstantinides S et al, ESC 2014

Cosa dicono altre linee guida

- The British Thoracic Society, in their 2003 guidelines, suggested that outpatient treatment of pulmonary embolism may be considered if the patient is not unduly breathless, there are no medical or social contraindications, and there is an efficient protocol in place.
- In 2012, the American College of Chest Physicians in their Evidence-Based Clinical Practice Guidelines, suggested early discharge of patients with low-risk pulmonary embolism whose home circumstances are adequate.
- Outpatient treatment of low-risk patients with PE should be restricted to hospitals with an available dedicated thrombosis clinic including a 24-h service to follow patients and to rapidly re-admit them in case of complications and to patients with well-maintained living conditions, strong support from family or friends, phone access, and ability to quickly return to the hospital if there is deterioration
- In 2016, the recommendation was modified to state that appropriately selected patients may be treated entirely at home rather than just discharged early.

British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. Thorax. 2003;58:470-483.

Keaton C, Akl EA, Ornelas T, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149: 315-352.

Hestia Citeria

1. Hemodynamically unstable?*
2. Thrombolysis or embolectomy necessary?
3. Active bleeding or high risk of bleeding?†
4. Oxygen supply to maintain oxygen saturation > 90% > 24 h?
5. Pulmonary embolism diagnosed during anticoagulant treatment?
6. Intravenous pain medication > 24 h?
7. Medical or social reason for treatment in the hospital > 24 h?
8. Creatinine clearance of less than 30 mL/min?‡
9. Severe liver impairment?§
10. Pregnant?
11. Documented history of heparin-induced thrombocytopenia?

If one of the questions is answered with **YES**,
The patient can NOT be treated at home

*Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure < 100 mmHg with heart rate > 100 beats per minute; condition requiring admission to an inten-

Zondag et al JTH 2011

Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism

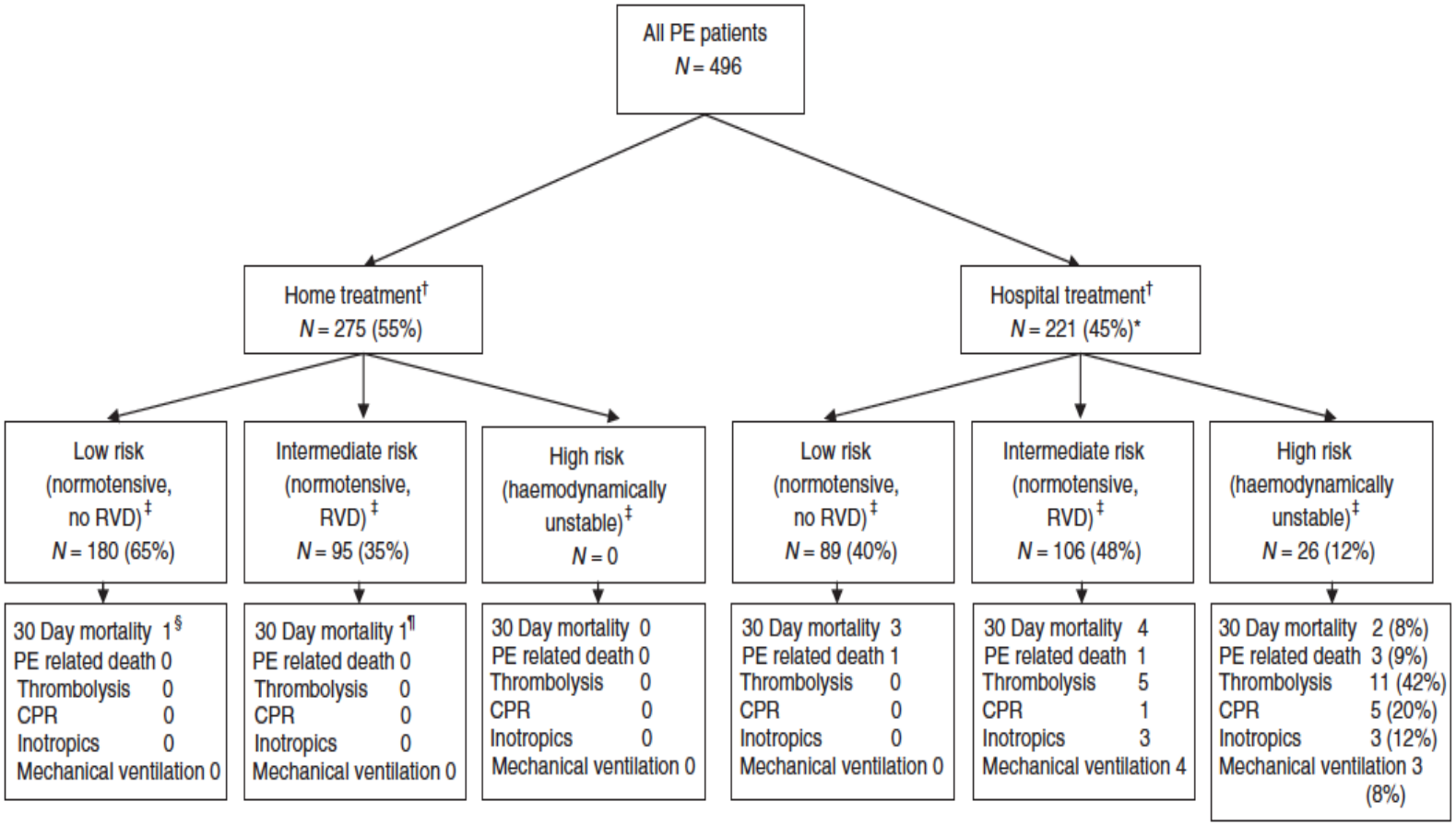
Wendy Zondag[1]*; Paul L. den Exter[1]*; Monique J. T. Crobach[2]; Anneke Dolsma[3]; Marjolein L. Donker[4]; Michiel Eijsvogel[5]; Laura M. Faber[6]; Herman M. A. Hofstee[7]; Karin A. H. Kaasjager[8]; Marieke J. H. A. Kruip[9]; Geert Labots[10]; Christian F. Melissant[11];

Table 2: sPESI items in patients at home versus patients treated in the hospital.

Characteristics of sPESI	All patients N=468	Home treatment N=247*	Hospital treatment N=221**
Age >80	43 (9)	9 (4)	34 (15)
History of cancer	69 (15)	21 (9)	48 (22)
Cardiopulmonary co-morbidity	47 (10)	12 (5)	35 (16)
Heart rate ≥110/min	76 (16)	22 (9)	54 (24)
Systolic blood pressure <100 mmHg	18 (4)	0	18 (8)
Oxygloblin saturation <90%	33 (7)	2 (0.8)	31 (14)
sPESI low risk	275 (59)	189 (77)	86 (39)
sPESI high risk	193 (41)	58 (23)	135 (61)

Data are displayed as N(%). * 50 patients were excluded because one or more items of the sPESI score were missing. ** 12 patients were excluded because one or more items of the sPESI score were missing.

Fenomeno HESTIA
Score clinico vs strumentale



RVD = right ventricular dysfunction measured on CT

*3 hospital patients were lost to follow-up (1 low risk and 2 intermediate risk); †according to Hestia criteria; ‡according to ESC criteria; §patient with fatal intracranial bleeding; ¶patient died of end-stage pancreatic cancer

Efficacy and Safety of Outpatient Treatment Based on the Hestia Clinical Decision Rule with or without N-Terminal Pro-Brain Natriuretic Peptide Testing in Patients with Acute Pulmonary Embolism. A Randomized Clinical Trial.

- Randomized 550 patients. 17 Dutch hospitals. . In the NT-proBNPgroup, 34 of 275 (12%) had elevated NT-proBNPvalues and were managedasinpatients.
- The primary endpoint (PE- or bleeding-related mortality,) occurred in none of the 275 patients (0%; 95% CI, 0-1.3%) subjected to NT-pro BNP testing, versus in 3 of 275 patients (1.1%; 95% CI, 0.2-3.2%) in the direct discharge group (P = 0.25).
- During the 3-month follow-up, recurrent venous thromboembolism occurred in two patients (0.73%; 95% CI, 0.1-2.6%) in the NT-proBNP group versus three patients (1.1%; 95% CI, 0.2-3.2%) in the direct discharge group (P = 0.65).

DenExter et al. Am J RespirCrit Care Med. 2016 Oct 15;194(8):998-1006.

CEEM Clinical and Experimental Emergency Medicine

Clin Exp Emerg Med 2016;3(3):126-131
http://dx.doi.org/10.15441/ceem.15.096

CrossMark

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Original Article

Admission rates for emergency department patients with venous thromboembolism and estimation of the proportion of low risk pulmonary embolism patie

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ceived: 1 March 2016
vised: 2 May 2016
cepted: 3 May 2016

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Table 1. Patient characteristics

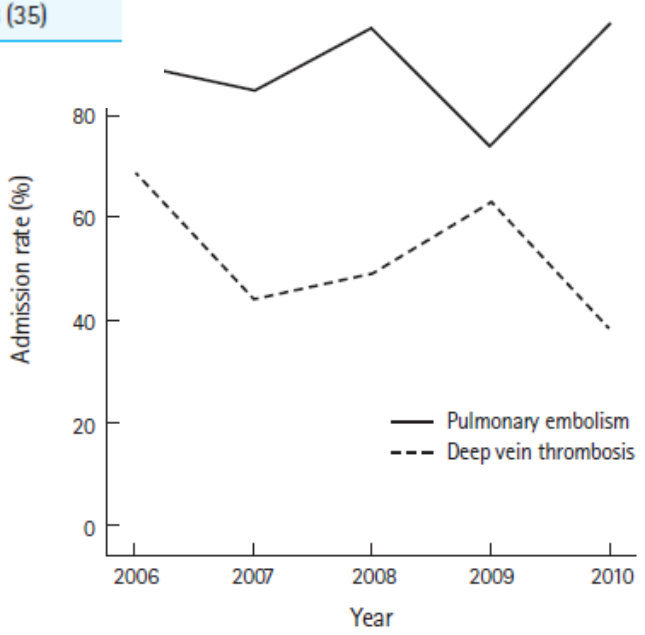
Characteristics	Deep vein	
Female	326,9	
Mean age (SE)	58 (1.8)	61 (2.0)
Race/ethnicity		
Non-Hispanic white	466,540 (72)	290,119 (74)
Non-Hispanic black	126,593 (19)	79,749 (20)
Hispanic	57,764 (9)	20,614 (5)
Other	1,363 (< 1)	3,546 (1)
Admitted	335,873 (52)	355,452 (90)
Intensive care unit	9,589 (2)	61,508 (16)
Died in emergency department	0 (0)	15,001 (4)

Values are presented as number (%) unless otherwise indicated.

Table 2. Anticoagulants prescribed while in emergency department

Anticoagulant	Deep vein thrombosis	Pulmonary embolism
Fondaparinux	1,802 (0.3)	2,208 (0.6)
Warfarin	136,725 (21)	39,825 (10)
Enoxaparin	299,125 (46)	136,535 (35)
Heparin	83,374 (13)	139,228 (35)

Values are presented as number (%).



Ruolo dei nuovi anticoagulanti

Drug	Trial	Design	Treatments and dosage	Duration	Patients	Efficacy outcome (results)	Safety outcome (results)
Dabigatran	RE-COVER[293]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2539 patients with acute VTE	Recurrent VTE or fatal PE: 2.4% under dabigatran vs. 2.1% under warfarin	Major bleeding: 1.6% under dabigatran vs. 1.9% under warfarin
	RE-COVER II[294]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2589 patients with acute VTE	Recurrent VTE or fatal PE: 2.3% under dabigatran vs. 2.2% under warfarin	Major bleeding: 15 patients under dabigatran vs. 22 patients under warfarin
Rivaroxaban	EINSTEIN-DVT[295]	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	3449 patients with acute DVT	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 3.0% under warfarin	Major or CRNM bleeding 8.1% under rivaroxaban vs. 8.1% under warfarin
	EINSTEIN-PE[296]	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	4832 patients with acute PE	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 1.8% under warfarin	Major or CRNM bleeding: 10.3% under rivaroxaban vs. 11.4% under warfarin
Apixaban	AMPLIFY[297]	Double-blind, double-dummy	Apixaban (10 mg b.i.d. for 7 days, then 5 mg b.i.d.) vs. enoxaparin/warfarin	6 months	5395 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 2.3% under apixaban vs. 2.7% under warfarin	Major bleeding: 0.6% under apixaban vs. 1.8% under warfarin

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Home Treatment of Pulmonary Embolism in the Era of Novel Oral Anticoagulants

Paul D. Stein, MD,[a] Fadi Matta, MD,[a] Patrick G. Hughes, DO,[a,b,c] Zak N. Hourmouzis, MD,[b] Nina P. Hourmouzis, MD,[b] Rachel M. White, DO,[a,d] Martina M. Ghiardi, DO,[c] Matthew A. Schwartz, MD,[e] Hillary L. Moore, MD,[e] Jennifer A. Bach, DO,[f] Robert E. Schweiss, DO,[f] Viviane M. Kazan, MD,[e] Edward J. Kakish, DO,[e] Daniel C. Keyes, MD,[a,f] Mary J. Hughes, DO[a,d]

[a]*Department of Osteopathic Medical Specialties, College of Osteopathic Medicine, Michigan State University, East Lansing;* [b]*Department of*

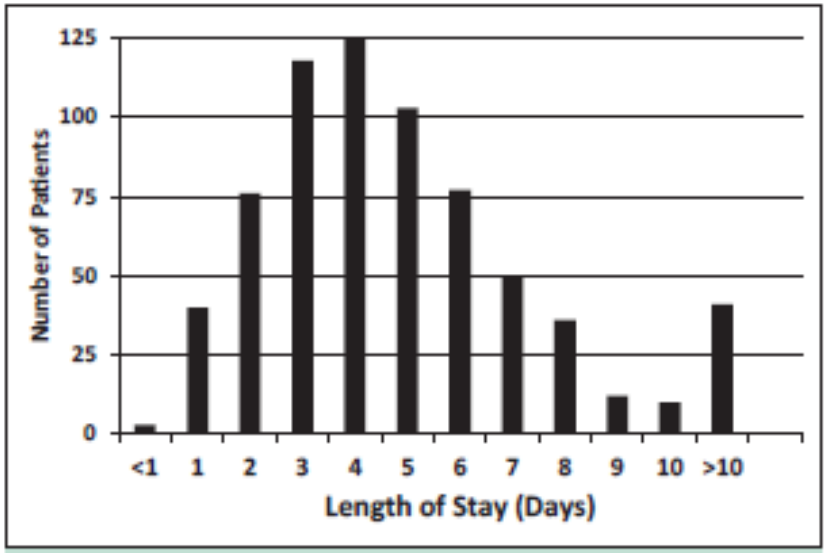


Figure Length of hospital stay of stable, nonhypoxic patients with pulmonary embolism.

CLINICAL SIGNIFICANCE

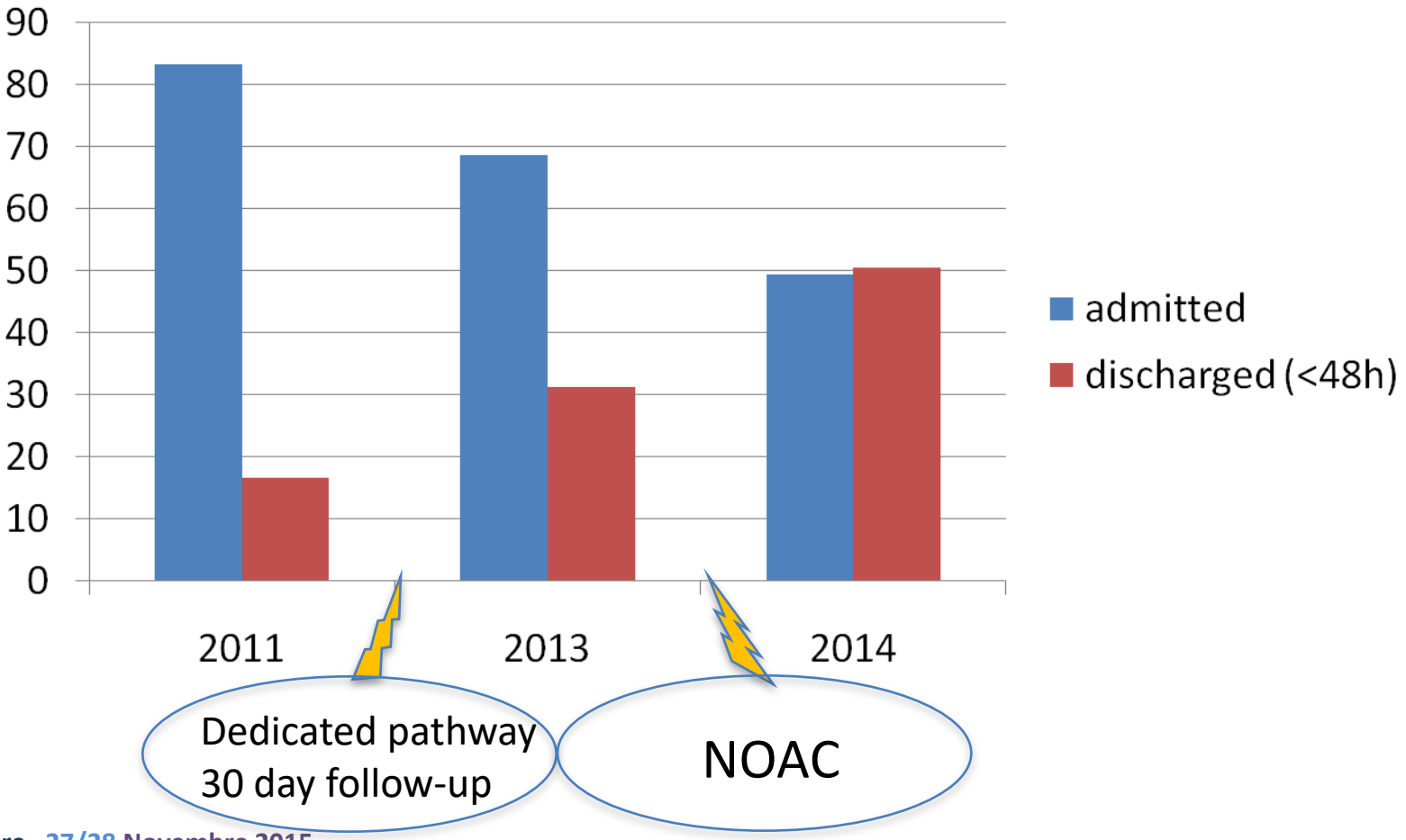
- Even in the era of novel oral anticoagulants, the vast majority of patients with acute pulmonary embolism were hospitalized.
- Only a small proportion of hospitalized patients with pulmonary embolism were discharged in ≤2 days. **16.2%**
- Novel oral anticoagulants were administered to less than one-third of patients with pulmonary embolism treated entirely at home or discharged early.

129, 2016

L’esperienza del centro di riferimento regionale toscano per la diagnosi e terapia della EP

- La gestione domiciliare (entro 48 ore) è possibile?
- E’ sicura?
- Quale score è più efficiente?
  - Numero di pazienti home treatment
  - Incidenza di eventi

Managment of PE patients AOU-Careggi ED (~120 pt/year)



Home treatment of patients with pulmonary embolism: The experience of the Tuscany referral center

S. Vanni, V.T. Stefanone, F. Mannucci, G Cerini , G Viviani, S Bigiarini, F Trausi, C Gigli, G Pepe, S. Grifoni

Emergency Department, Aou-Careggi, Firenze, Italia

- **Efficacia** della stratificazione del rischio: confronto PESI, sPESI, Hestia e Criterio Clinico:
  Giudizio clinico + RVD (comorbidità, compliance, setting familiare)

- **Sicurezza** della terapia domiciliare secondo la stratificazione del rischio: follow-up di eventi avversi (recidiva TEV, decesso, emorragie maggiori) a 1 mese

Gennaio 2014- Giugno 2016
presso DEA dell'AOU di
Careggi

884 sospette EP

288 casi di EP

11 casi esclusi per assenza di consenso

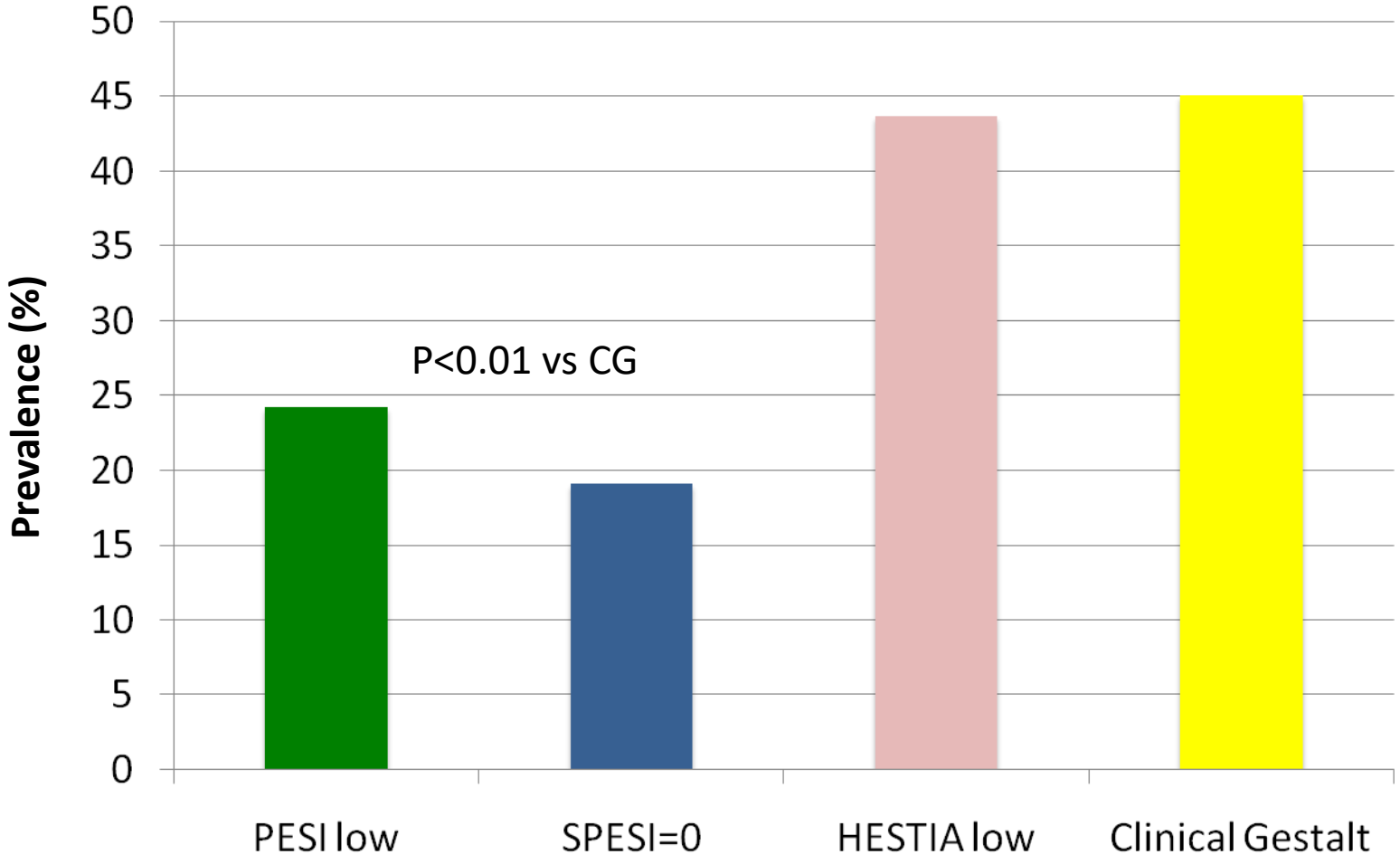
Trattamento domiciliare
145 (52.3%)

Morte a un mese per qualsiasi causa
5 (3.4%)

Trattamento Ospedaliero
132 (48.7%)

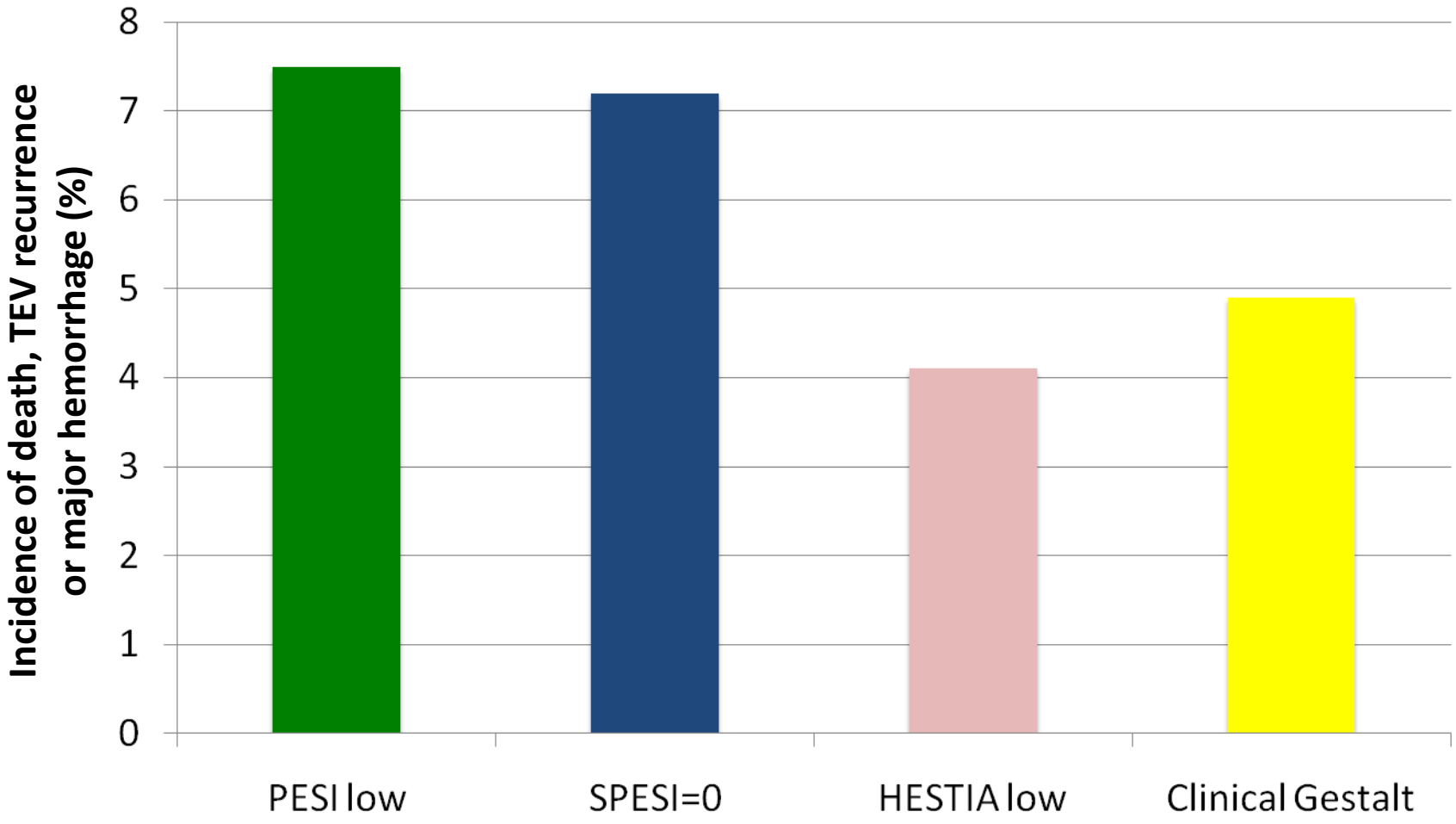
Morte a un mese per qualsiasi causa
15 (11.3%)

Confronto dell' efficienza dei vari metodi



Vanni S et al ESC congress 2016

Confronto “sicurezza” dei vari metodi



Vanni S et al ESC congress 2016

Home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban

Rationale and design of the HoT-PE Trial

Stefano Barco[1]; Mareike Lankeit[1]; Harald Binder[2]; Sebastian Schellong[3]; Michael Christ[4]; Jan Beyer-Westendorf[5]; Daniel Duerschmied[6]; Rupert Bauersachs[7]; Klaus Empen[8]; Matthias Held[9]; Martin Schwaiblmair[10]; Cândida Fonseca[11]; David Jiménez[12]; Cecilia Becattini[13]; Kurt Quitzau[1]; Stavros Konstantinides[1,14]

[1]Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University, Mainz, Germany; [2]Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at the University Medical Center Mainz, Germany; [3]Municipal Hospital of Dresden-Friedrichstadt, Dresden, Germany; [4] Department of Emergency and

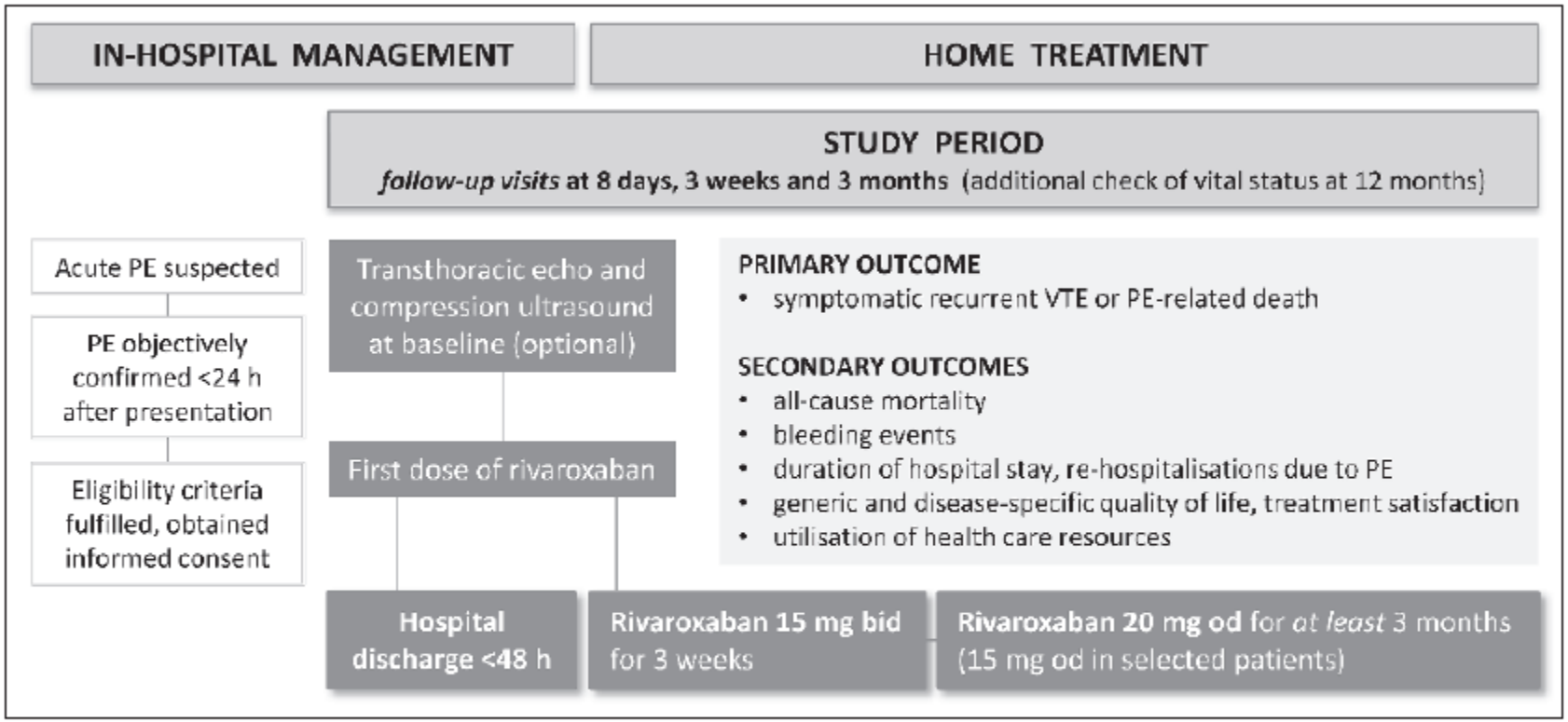


Figure 1: Study design. VTE, venous thromboembolism; PE, pulmonary embolism; od, once daily; bid, twice daily.


Tra dire e il fare c’è di mezzo...
il cominciare
Pier Luigi Ricci