Πνευμονική Κυκλοφορία

Τι νεώτερο

Ι Μητρούσκα

Πνευμονολογική Κλινική

Πανεπιστημιακό Νοσοκομείο Κρήτης

Outpatients versus inpatient treatment with acute pulmonary embolism: *an international, open-label, randomized, non-inferiority trial*

Aujesky D Lancet 2011;578:41-48

Methods

Study design and participants

- 19 emergency departments
- Adults (>18 years of age)
- Acute, symptomatic and objectively verified pulmonary embolism
  - *Low risk of death (PE severity index risk classes I or II)*

	Points assigned
Age	+1 per year
Male sex	+10
Cancer*	+30
Heart failure	+10
Chronic lung disease	+10
Pulse ≥110 beats per min	+20
Systolic blood pressure <100 mm Hg	+30
Respiratory rate ≥30 breaths per min	+20
Temperature <36°C	+20
Altered mental status†	
Arterial oxygen saturation <90%‡	

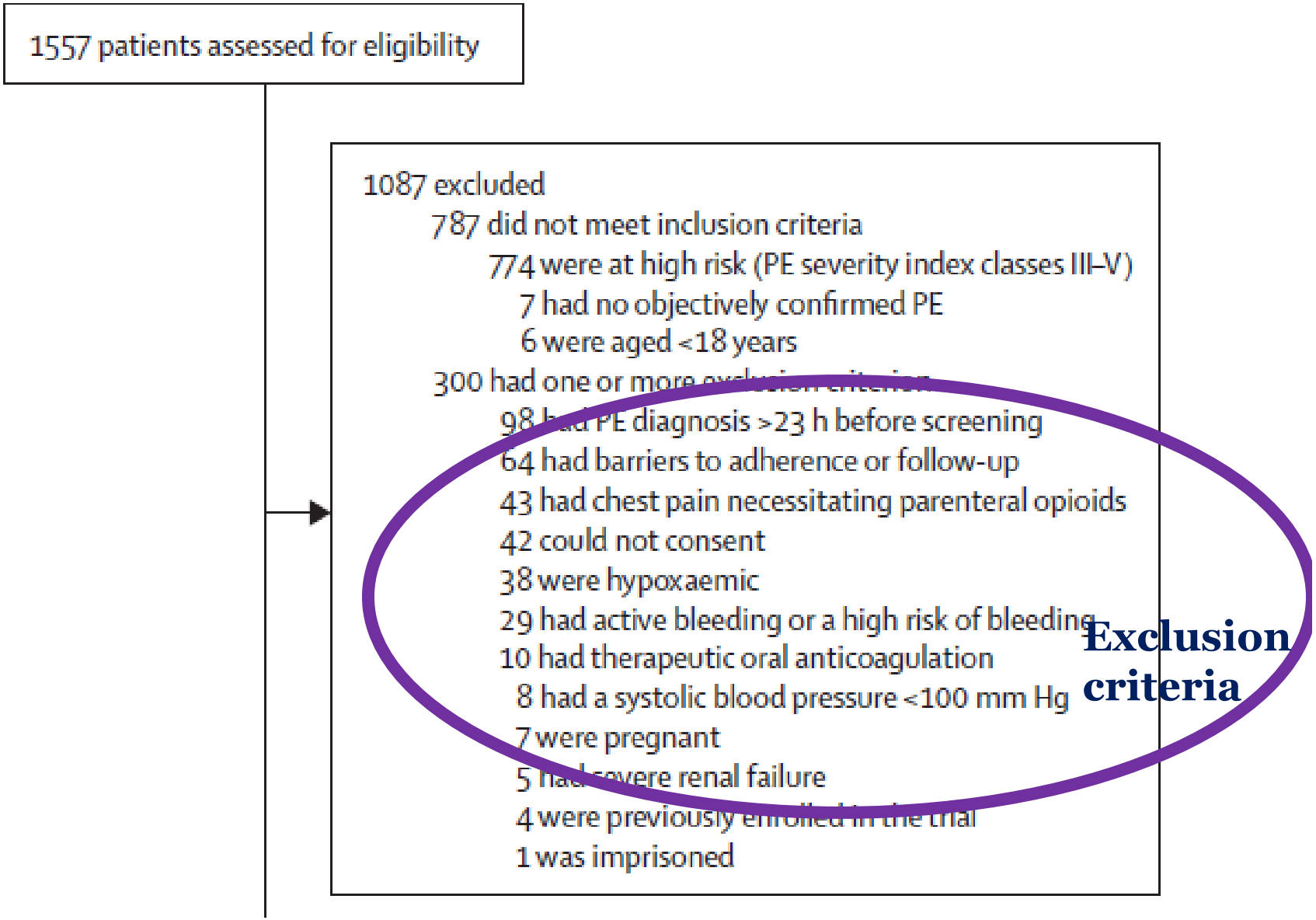
Score of < 66 is risk class I
66-85 risk class II
86-105 risk class III
106-125 risk class IV
>125 risk class V

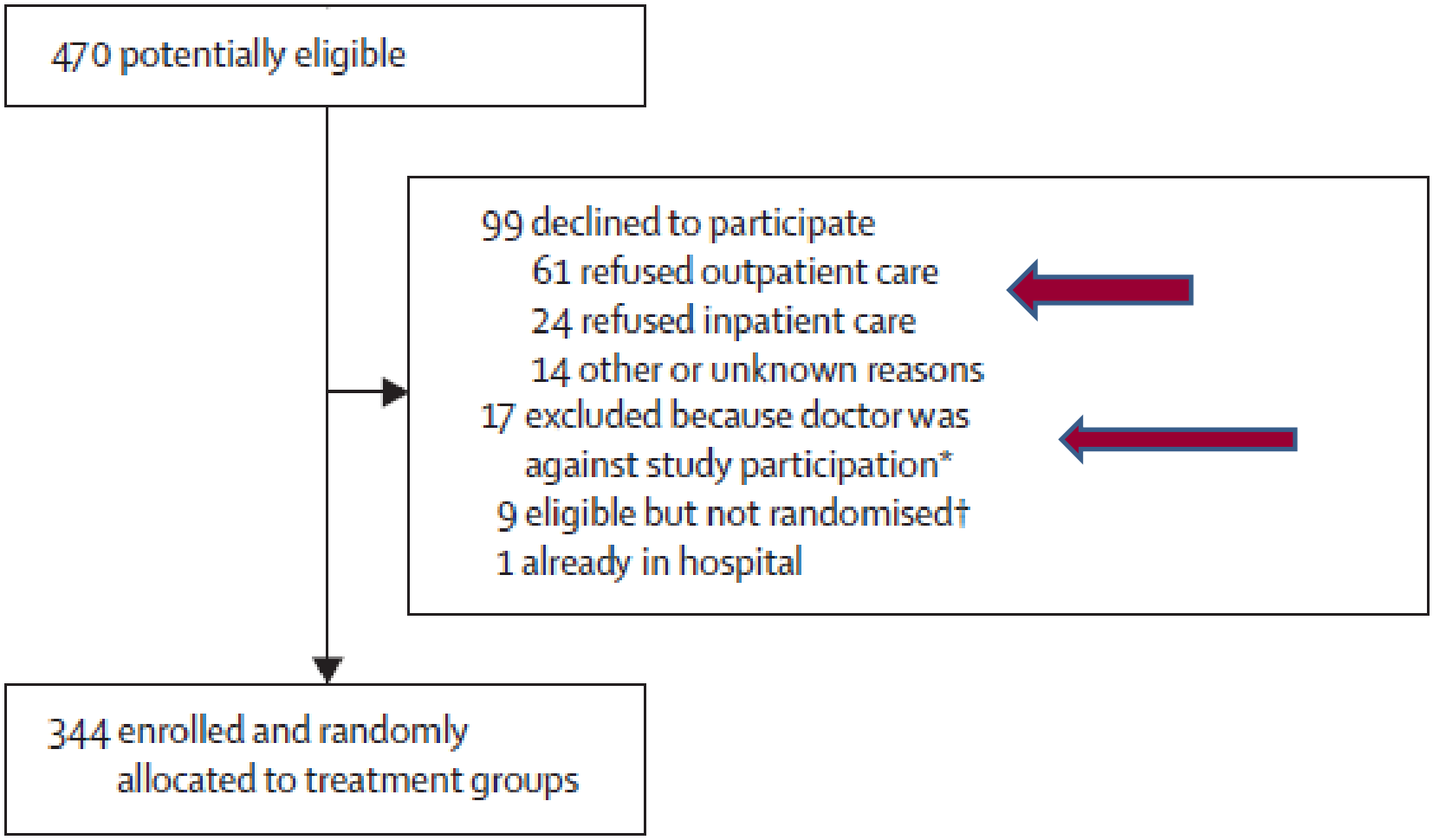
Methods

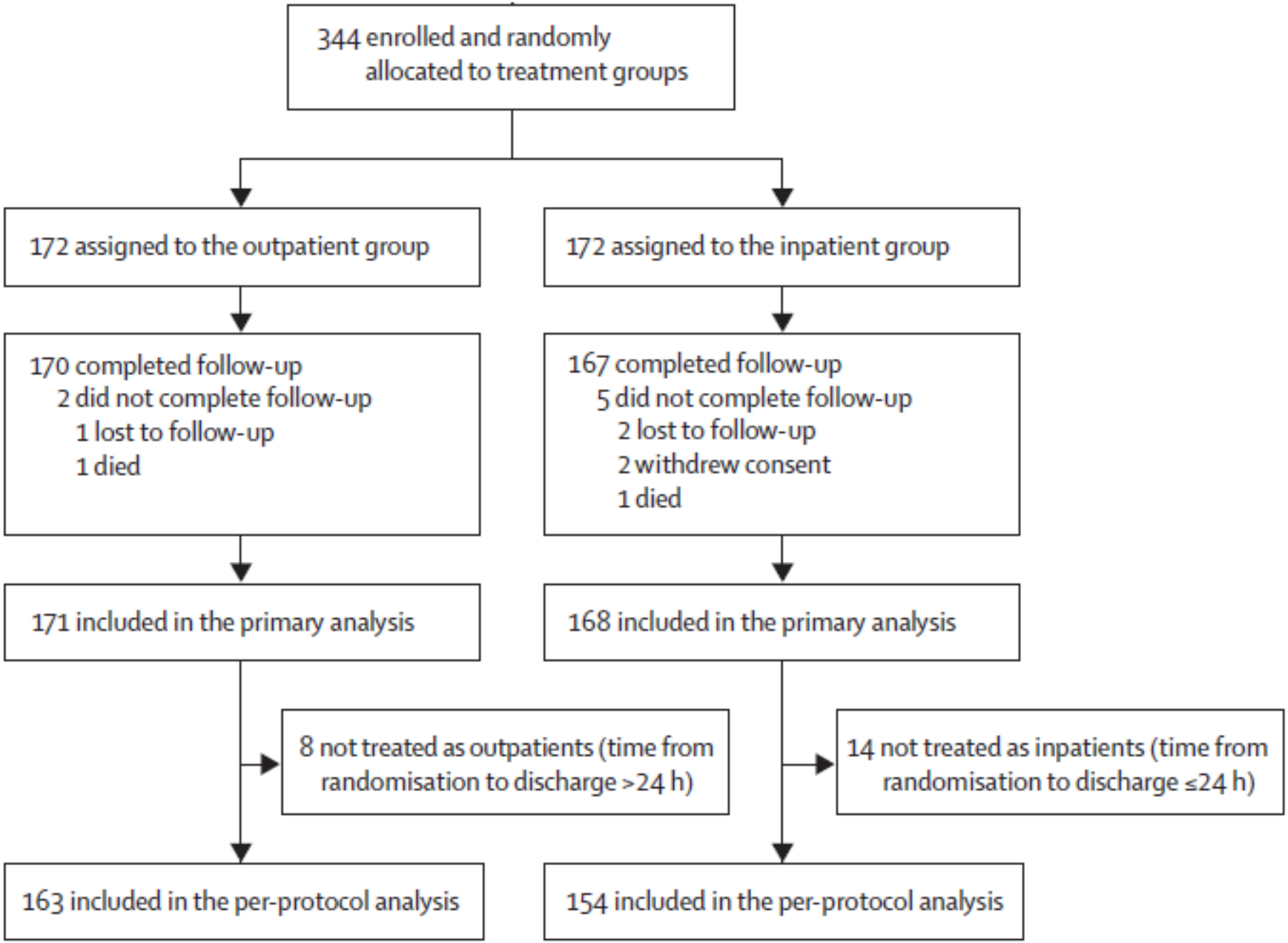
Study design and participants

- 19 emergen
- Adults
- Acut ified pulmo
  - *Low risk o lasses I or II*
- Computer-generated randomization sequence in 1:1 ratio to initial outpatient
  - *Discharged from hospital 24h after randomization*

Enoxaparin/VCA


1557 patients assessed for eligibility
1087 excluded
787 did not meet inclusion criteria
774 were at high risk (PE severity index classes III–V)
7 had no objectively confirmed PE
6 were aged <18 years
300 had one or more exclusion criterion
98 had PE diagnosis >23 h before screening
64 had barriers to adherence or follow-up
43 had chest pain necessitating parenteral opioids
42 could not consent
38 were hypoxaemic
29 had active bleeding or a high risk of bleeding
10 had therapeutic oral anticoagulation
8 had a systolic blood pressure <100 mm Hg
7 were pregnant
5 had severe renal failure
4 were previously enrolled in the trial
1 was imprisoned
Exclusion criteria


470 potentially eligible
99 declined to participate
61 refused outpatient care
24 refused inpatient care
14 other or unknown reasons
17 excluded because doctor was against study participation*
9 eligible but not randomised†
1 already in hospital
344 enrolled and randomly allocated to treatment groups


344 enrolled and randomly allocated to treatment groups
172 assigned to the outpatient group
172 assigned to the inpatient group
170 completed follow-up
2 did not complete follow-up
1 lost to follow-up
1 died
167 completed follow-up
5 did not complete follow-up
2 lost to follow-up
2 withdrew consent
1 died
171 included in the primary analysis
168 included in the primary analysis
8 not treated as outpatients (time from randomisation to discharge >24 h)
14 not treated as inpatients (time from randomisation to discharge ≤24 h)
163 included in the per-protocol analysis
154 included in the per-protocol analysis

- The primary outcome was:
  - ***symptomatic, recurrent venous tromboembolism within 90 days***

- Secondary clinical outcome:
  - *Safety outcome*
    - Including major bleeding within 14 or 90 days
  - *Mortality within 90 days*

Baseline characteristics

	Outpatient group (n=171)	Inpatient group (n=168)
Age (years)	47 (16)	49 (15)
Male sex	84 (49%)	85 (51%)
Race*		
White	129 (75%)	124 (74%)
Black	6 (4%)	6 (4%)
Asian	0	1 (1%)
Unknown	36 (21%)	37 (22%)
Body-mass index (kg/m^2)	26·1 (5·0)	26·8 (4·9)
Diagnostic method for index PE		
Spiral computed tomography	152 (89%)	150 (89%)
High-probability lung scanning	13 (8%)	9 (5%)
Pulmonary angiography	0	1 (1%)
Positive test for proximal deep vein thrombosis†	6 (4%)	8 (5%)

Baseline characteristics

	Outpatient group	Inpatient group
Localisation of PE‡		
Central	24 (14%)	16 (10%)
Lobar	60 (35%)	66 (39%)
Segmental	110 (64%)	100 (60%)
Subsegmental	52 (30%)	44 (26%)
Unspecified	29 (17%)	26 (15%)

Baseline characteristics

	Outpatient group	Inpatient group
Clinical findings		
New or worsening dyspnoea	129 (75%)	126 (75%)
Acute chest pain	121 (71%)	121 (72%)
Haemoptysis	12 (7%)	13 (8%)
Syncope	3 (2%)	5 (3%)
Symptoms of deep vein thrombosis††	51 (30%)	53 (32%)
Systolic blood pressure (mm Hg)	136 (18)	138 (18)
Heart rate (beats per min)	86 (14)	85 (15)
Respiratory rate (breaths per min)	19 (4)	19 (4)
Body temperature (°C)	36·9 (0·6)	36·9 (0·6)
Arterial oxygen saturation (%)‡‡	96 (2)	96 (2)

Results
Effectiveness and safety outcomes

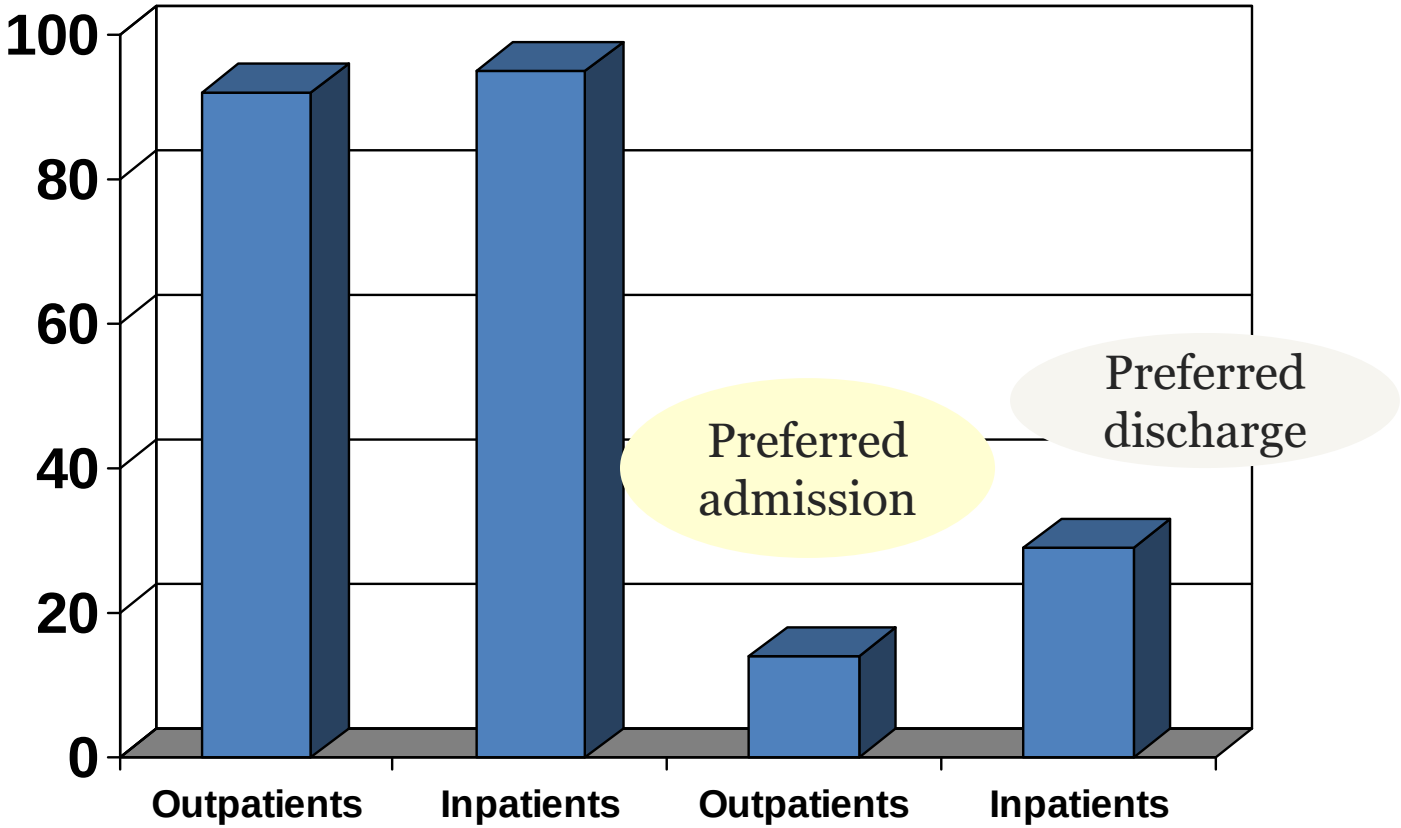
Primary analysis outcomes within 90 days†			
Recurrent VTE	1 (0·6%)‡	0	0·6%
Major bleeding	3 (1·8%)	0	1·8%
Intramuscular	2 (1·2%)	0	1·2%
Menometrorrhagia	1 (0·6%)	0	0·6%
Overall mortality	1 (0·6%)§	1 (0·6%)¶	0%
Primary analysis outcomes within 14 days†			
Recurrent VTE	0	0	0%
Major bleeding	2 (1·2%)	0	1·2%
Intramuscular	2 (1·2%)	0	1·2%
Menometrorrhagia	0	0	0%
Overall mortality	0	0	0%

Medical resources used by treatment group

	Outpatient group (n=171)	Inpatient group (n=168)	p value
Length of initial hospital stay (days)*	0·5 (1·0)	3·9 (3·1)	N/A
Treated entirely in the outpatient setting†	163 (95%)	14 (8%)	<0·0001
Hospital readmissions within 90 days			
All	18	23	0·60
Potentially venous thromboembolism-related‡	11	6	0·58
Emergency department visits within 90 days			
All	36	36	0·94
Potentially venous thromboembolism-related‡	27	19	0·51
Visits to a primary-care doctor within 90 days			
All	202	216	0·67
Potentially venous thromboembolism-related‡	112	92	0·58
Home nursing visits for enoxaparin injection within 90 days	348	105	0·53§

Satisfaction

14 days after randomization



Interpretation

- In selected low-risk patient with pulmonary embolism, outpatient care can safely and effectively be used in place of impatient care

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN investigators

N Engl J Med Dec 2010; 363:2499-510

Background

- Acute venous trhomboembolism is a common disorder
  - *DVT or P*
  - *1-*
- Sl
- Th

INR in the therapeutic range
57.7% of the time
Above 3.0 for 16.2% of the time
Below 2.0 for 24.4% of the time

ulation)

≈ 25%

erapy

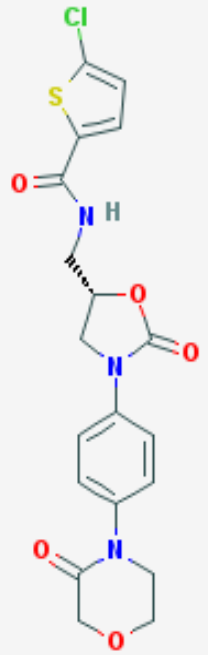
atment

ends

  - 5-10% during

- Rivaroxaban:
  - ***Αναστολέας του παράγοντα Χα***
  - ***Χορηγείται από το στόμα***
  - ***Απλό, καθορισμένης δόσης φάρμακο για τη θεραπεία της εν-τω βάθει θρόμβωσης και την συνέχιση της αγωγής***
  - ***Δεν απαιτείται τακτικός εργαστηριακός έλεγχος.***

Molecular Weight: 435.88132 [g/mol]
Molecular Formula: $C_{19}H_{18}ClN_3O_5S$



2 studies

- Open label
- Randomized
- Event-driven
- Non-inferiority study

- Double-blind
- Randomized
- Event-driven
- Superiority study

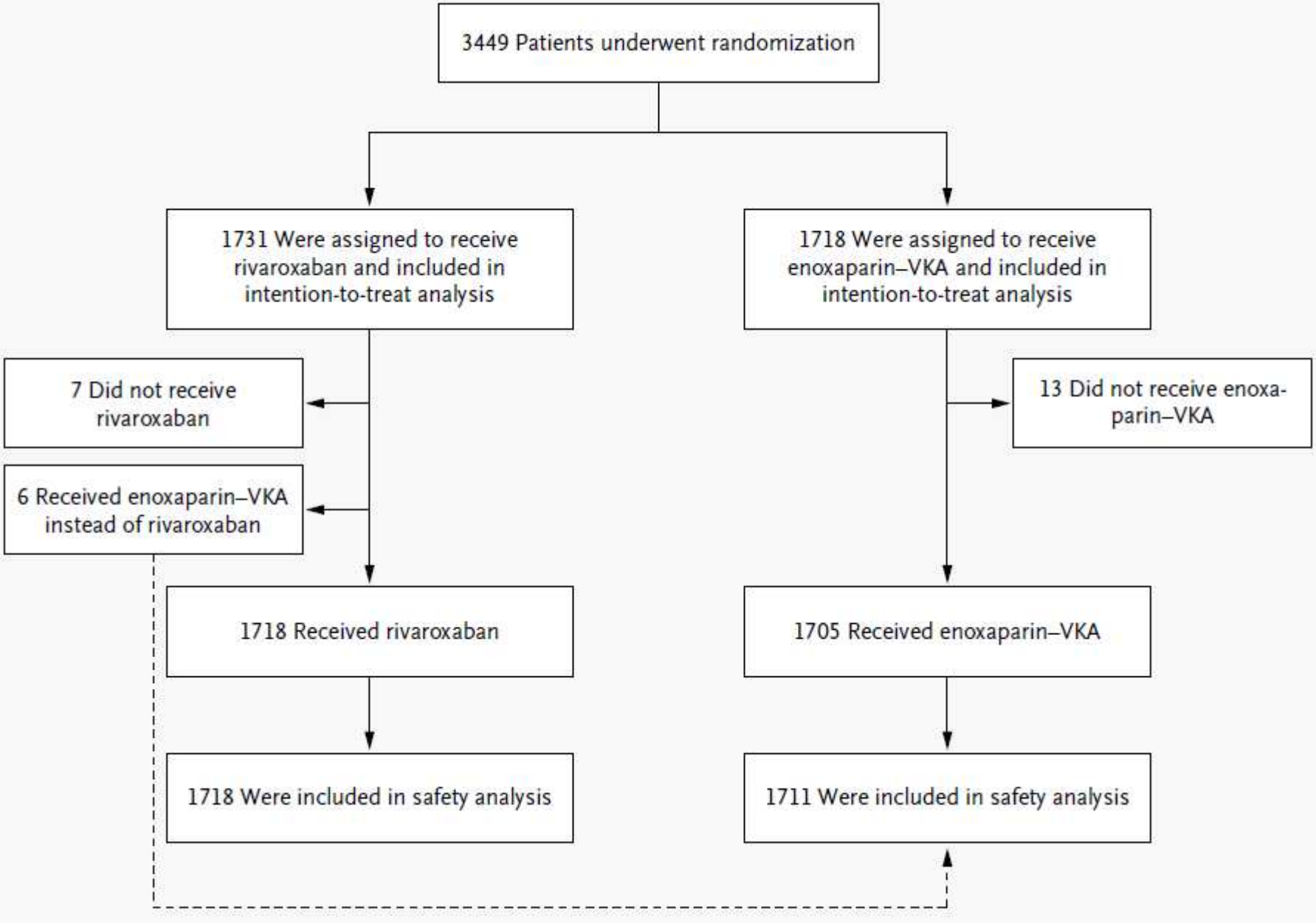
EINSTEIN program

- Three randomized trials of rivaroxaban:
  - One for the treatment of acute deep-vein thrombosis (the Acute DVT Study)
  - One for the treatment of acute pulmonary embolism (the Acute PE Study)
  - One for continued treatment in patients who have receive treatment for acute DVT or PE

Purpose of the study

- Primary efficacy outcome (for both studies)
  - ***Recurrent venous thromboembolism***
- Principal safety outcome
  - ***Major bleeding or clinically relevant non-major bleeding***
    - Initial-treatment study
  - ***Major bleeding***
    - In the continued-treatment study

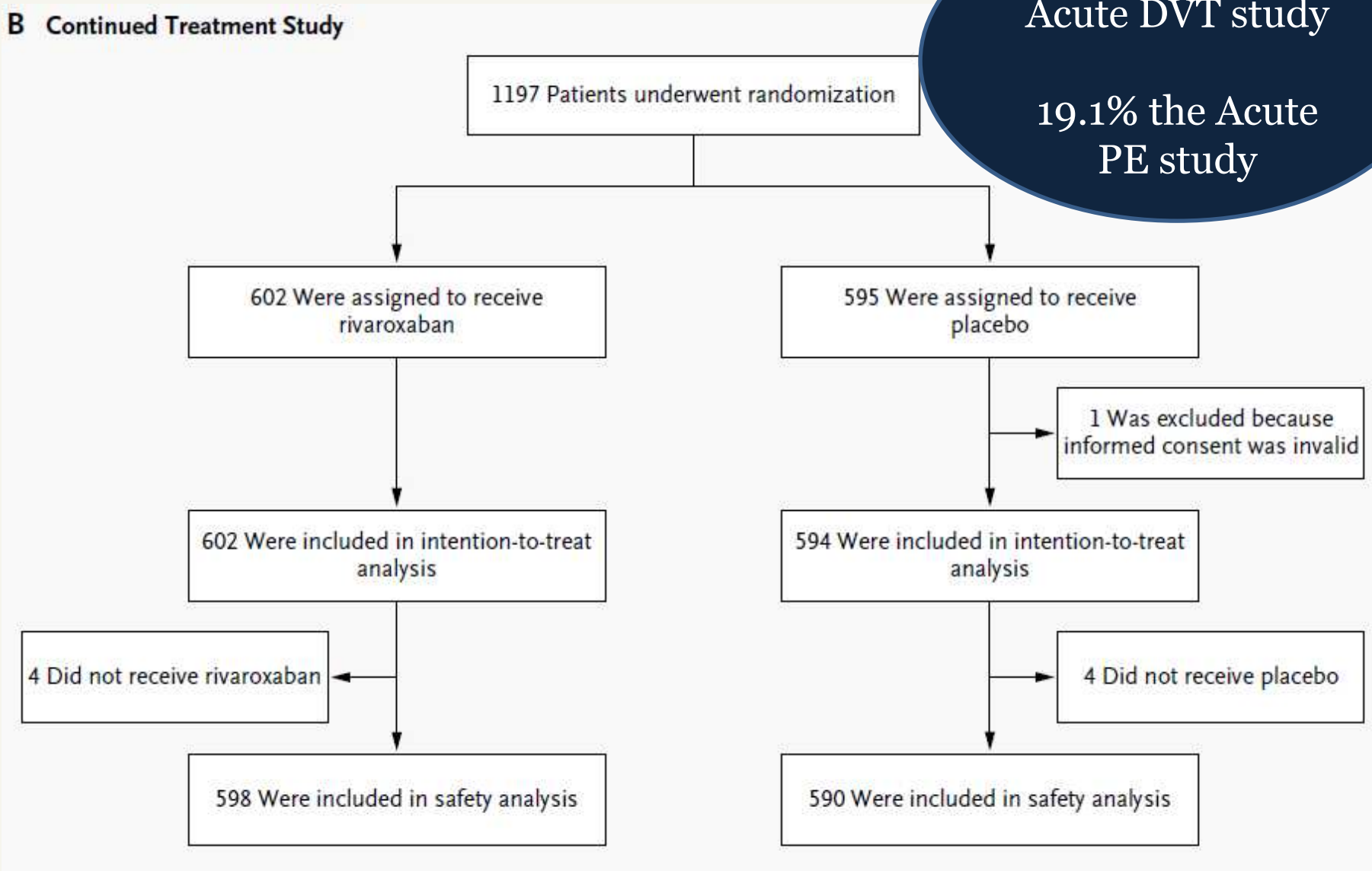
A Acute DVT Study



Superiority study

34.1% completed Acute DVT study

19.1% the Acute PE study

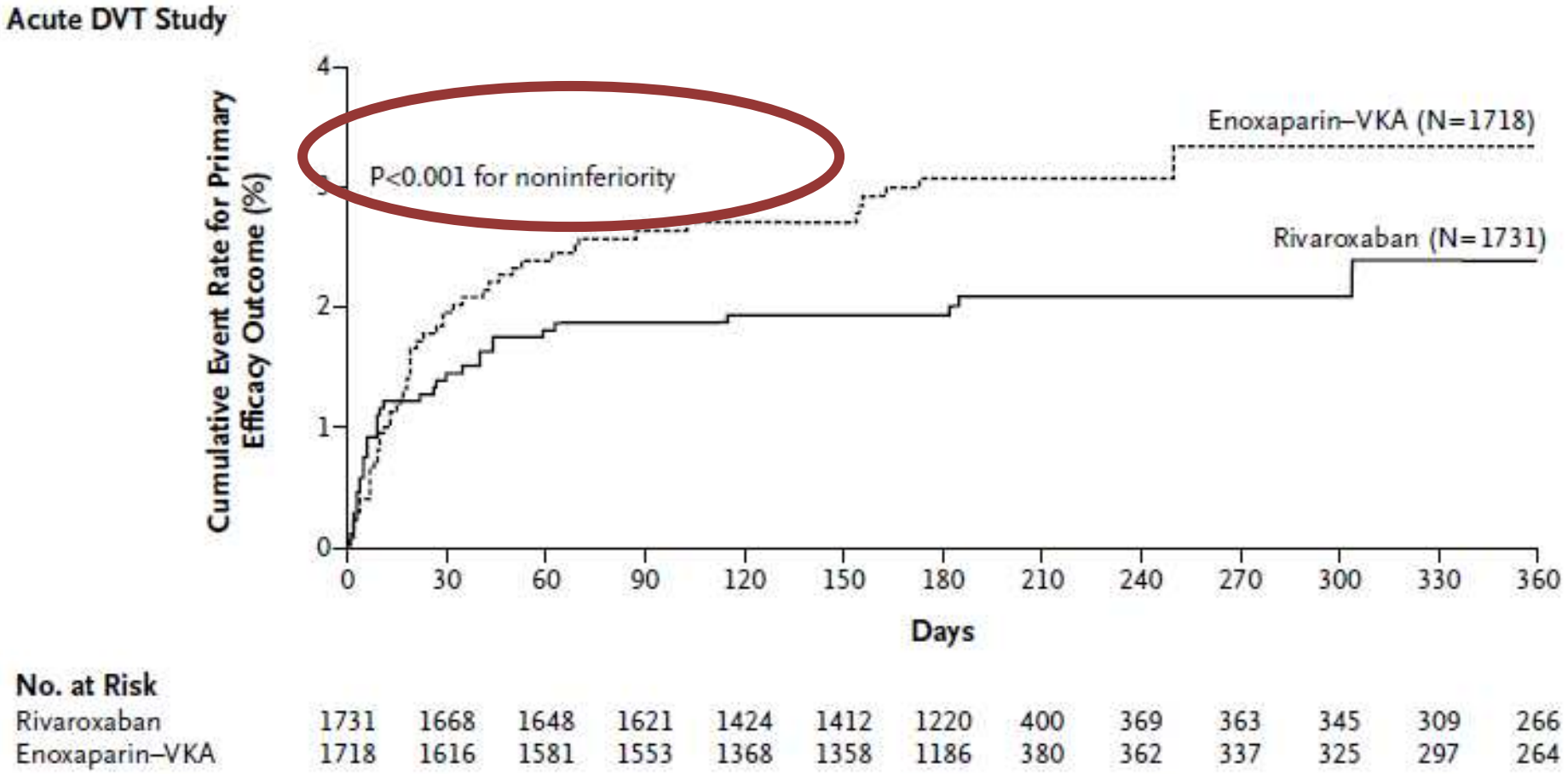


Clinical outcome
acute DVT study

Outcome	Rivaroxaban	Enoxaparin–VKA	P Value
Safety			
Safety population	1718	1711	
First major or clinically relevant nonmajor bleeding occurring during treatment	139 (8.1)	138 (8.1)	<0.001†
Major bleeding	14 (0.8)	20 (1.2)	
Contributing to death	1 (<0.1)	5 (0.3)	
In a critical site	3 (0.2)	3 (0.2)	
Associated with a fall in hemoglobin of ≥2 g per deciliter, transfusion of ≥2 units, or both	10 (0.6)	12 (0.7)	
Clinically relevant nonmajor bleeding	126 (7.3)	119 (7.0)	0.03
Total deaths through end of intended treatment period	38 (2.2)	49 (2.9)	

Time course of recurrent acute VT

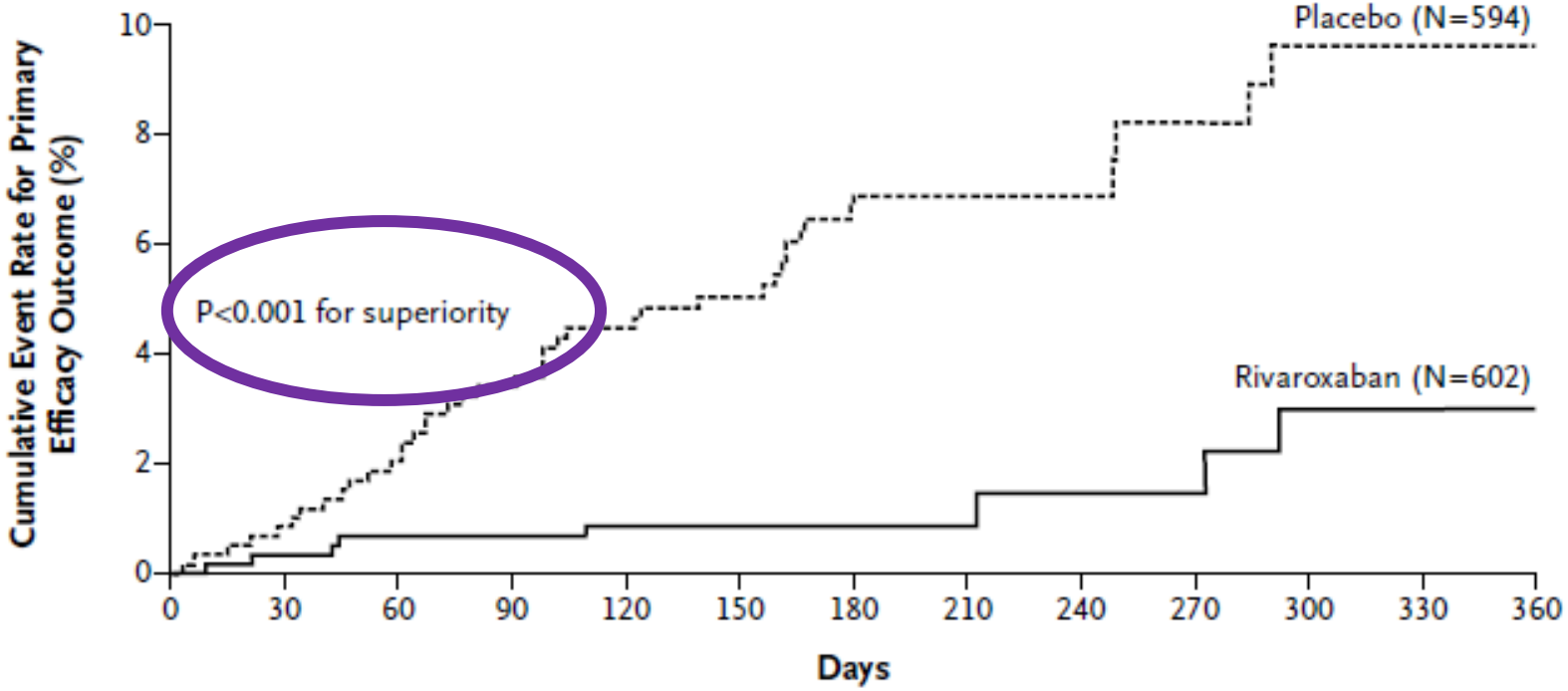
Kaplan-Maier



Time course of recurrent acute VT

Kaplan-Maier

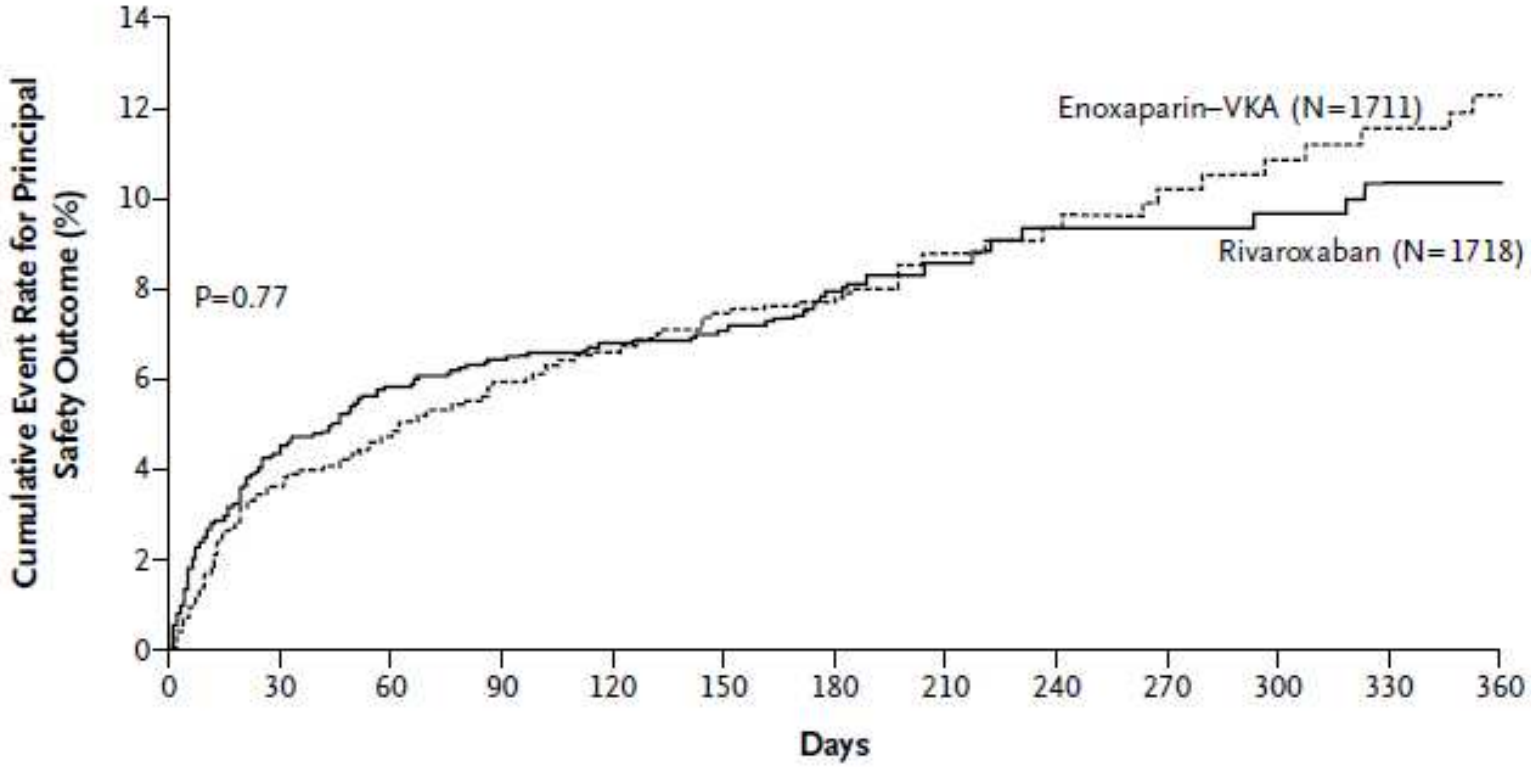
Continued Treatment Study



No. at Risk													
Rivaroxaban	602	590	583	573	552	503	482	171	138	132	114	92	81
Placebo	594	582	570	555	522	468	444	164	138	133	110	93	85

Principal safety outcome

first major or clinically relevant nonmajor bleeding



No. at Risk													
Rivaroxaban	1718	1585	1538	1382	1317	1297	715	355	338	304	278	265	140
Enoxaparin–VKA	1711	1554	1503	1340	1263	1238	619	338	321	287	268	249	118

Conclusions

- Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis

  that

  may improve the benefit-to-risk profile of anticoagulation

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Results from an international prospective registry

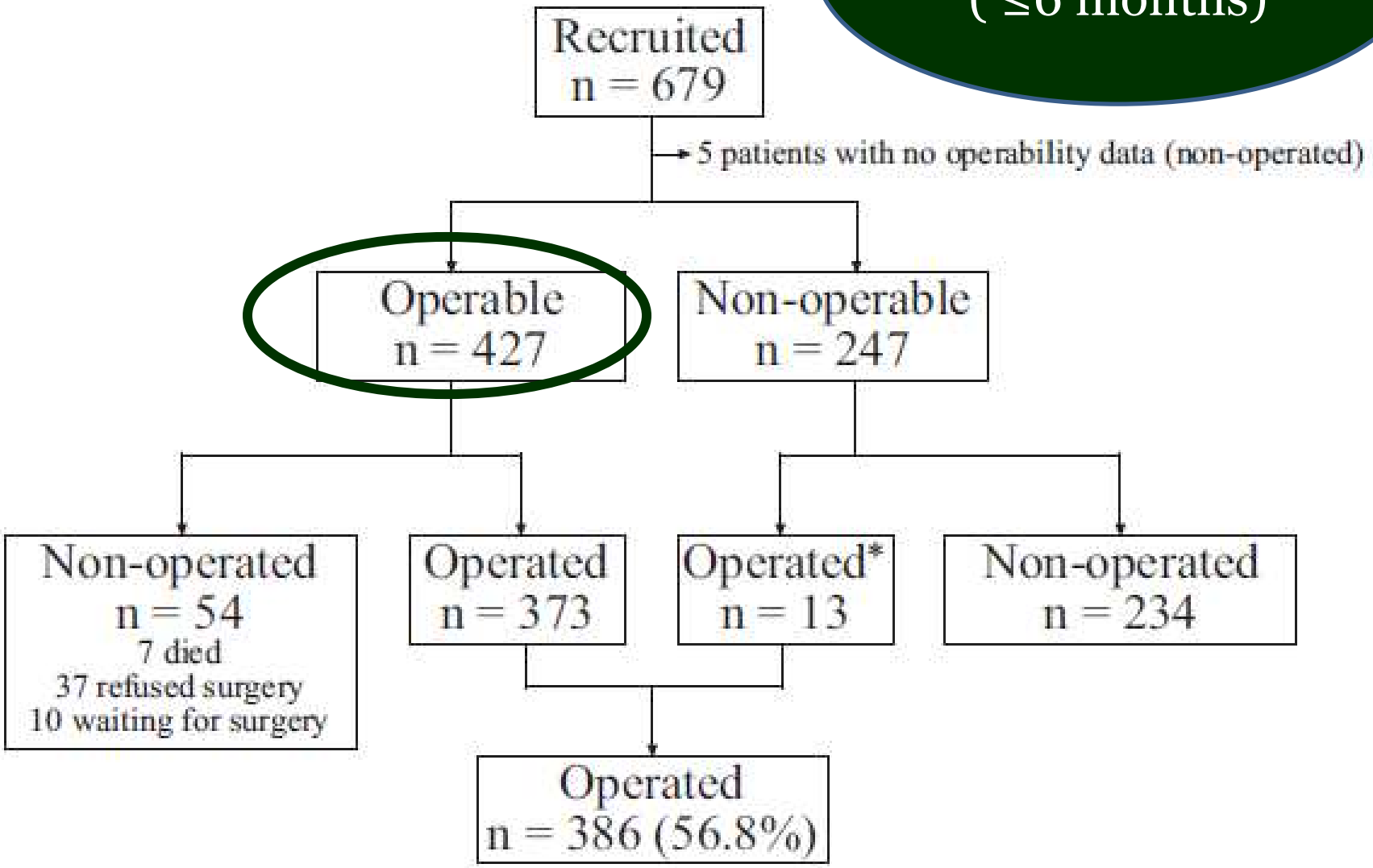
Pepke-Zepa j Circulation 2011 Oct 3

Background / purpose

- Chronic thromboembolic pulmonary hypertension (CTEPH) is often a sequel of venous thromboembolism with fatal natural history; however, many cases can be cured by pulmonary endarterectomy.

- The clinical characteristics and current management of patients enrolled in the international CTEPH registry was investigated

Newly diagnosed
(≤6 months)



Patients Characteristics at Diagnosis

	All Patients (n=679)	Operable Patients* (n=427)	Nonoperable Patients* (n=247)
Gender, % male	50.1	53.4	44.5
Ethnicity, % white	95.9	95.3	96.7
Age, y, median [Q1;Q3]	63 [51; 72]	61 [48; 70]	67 [57; 74]
Weight, kg, median [Q1;Q3]	75 [65; 87]	76 [66; 88]	73 [63; 82]
NYHA class, % I/II/III/IV	0.7/17.2/68.6/12.8	0.5/19.2/67.7/12.6	1.2/15.8/70.4/12.6
6MWD, m, median [Q1; Q3] (n)	329 [245; 427] (589)	340 [250; 435] (373)	315 [223; 400] (214)
Blood group non-0, % (n)	76.0 (366)	79.5 (249)	68.4 (117)

Patients History of Venous Thrombo-embolism

	All Patients (n=679)	Operable Patients* (n=427)	Nonoperable Patients* (n=247)	*P* (Exploratory)
Confirmed previous acute PE, % (n)	74.8 (678)	77.5 (427)	70.0 (247)	0.0344
PE diagnosed more than once, % (n)	32.8 (469)	35.0 (303)	28.8 (163)	0.2145
Size of previous PE reported as massive, % (n)	40.8 (240)	47.1 (155)	29.4 (85)	0.0090
Confirmed previous DVT, % (n)	56.1 (426)	60.4 (280)	49.0 (143)	0.0295
Acute PE and DVT, % (n)	55.4 (413)	59.3 (270)	48.9 (141)	0.0477
Acute PE no DVT, % (n)	42.6 (413)	39.3 (270)	48.2 (141)	0.0926
Thrombolytic treatment, % (n)	14.4 (404)	18.5 (265)	6.6 (137)	0.0009
Vena cava filter implanted, % (n)	12.4 (491)	13.7 (322)	10.2 (166)	0.3139

Diagnosis Evaluation

	All Patients (n=679)	Operable Patients* (n=427)	Nonoperable Patients* (n=247)
Right heart catheterization			
mPAP†, mm Hg, median [Q1; Q3] (n)	47 [38; 55] (669)	47 [38; 55] (423)	47 [38; 55] (244)
PVR‡, dyn · s · cm^{-5}, median [Q1; Q3] (n)	709 [480; 988] (604)	717 [495; 963] (381)	691 [426; 1051] (221)
Cardiac index, L · min^{-1} · m^{-2} median [Q1;Q3] (n)	2.2 [1.8; 2.7] (632)	2.2 [1.8; 2.7] (404)	2.3 [1.8; 2.8] (227)
Scintigraphy, % (n)			
Perfusion scan abnormal	98.7 (535)	99.4 (344)	97.4 (189)
Ventilation scan abnormal	19.0 (484)	17.5 (314)	22.0 (168)
Angiography, % (n)			
Proximal lesions	63.0 (552)	70.9 (358)	48.2 (191)
CT scan, % (n)			
Proximal lesions	60.4 (541)	70.1 (345)	43.0 (193)
Dilation of bronchial arteries	68.4 (345)	75.0 (216)	57.0 (128)
Mosaic perfusion pattern	76.6 (414)	82.4 (261)	67.1 (152)

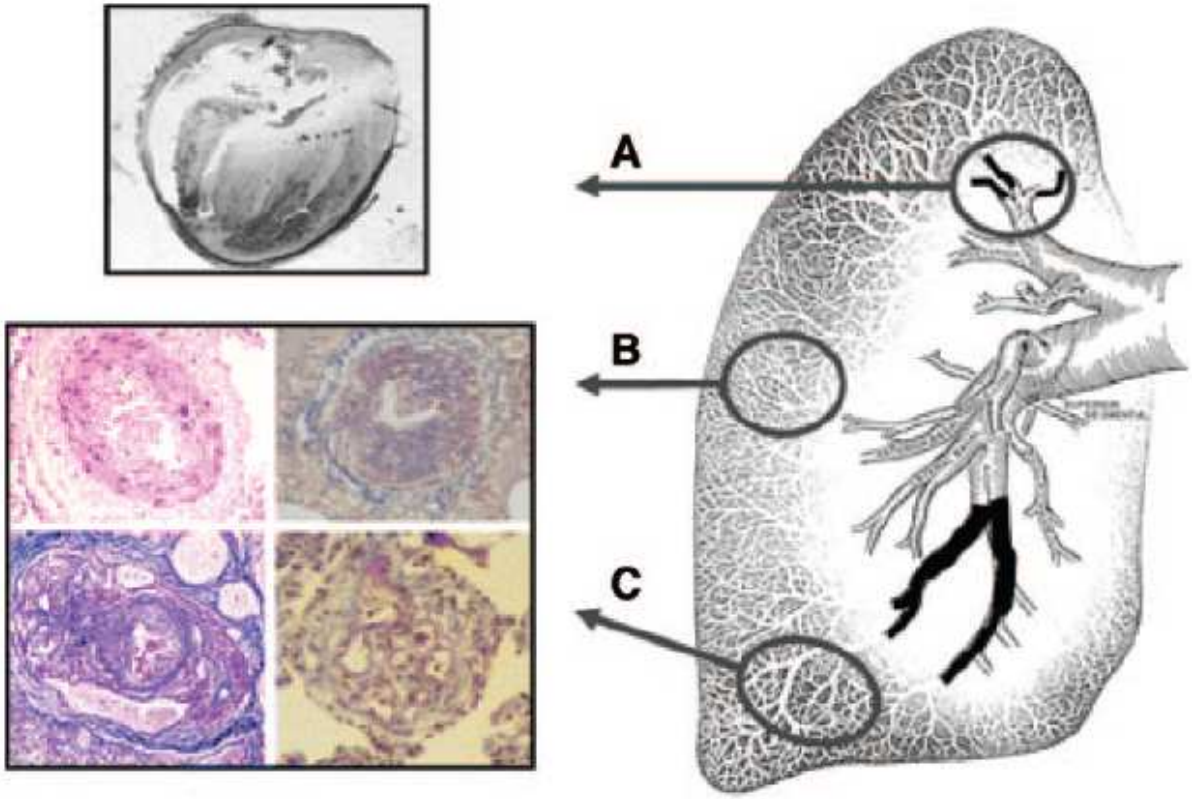
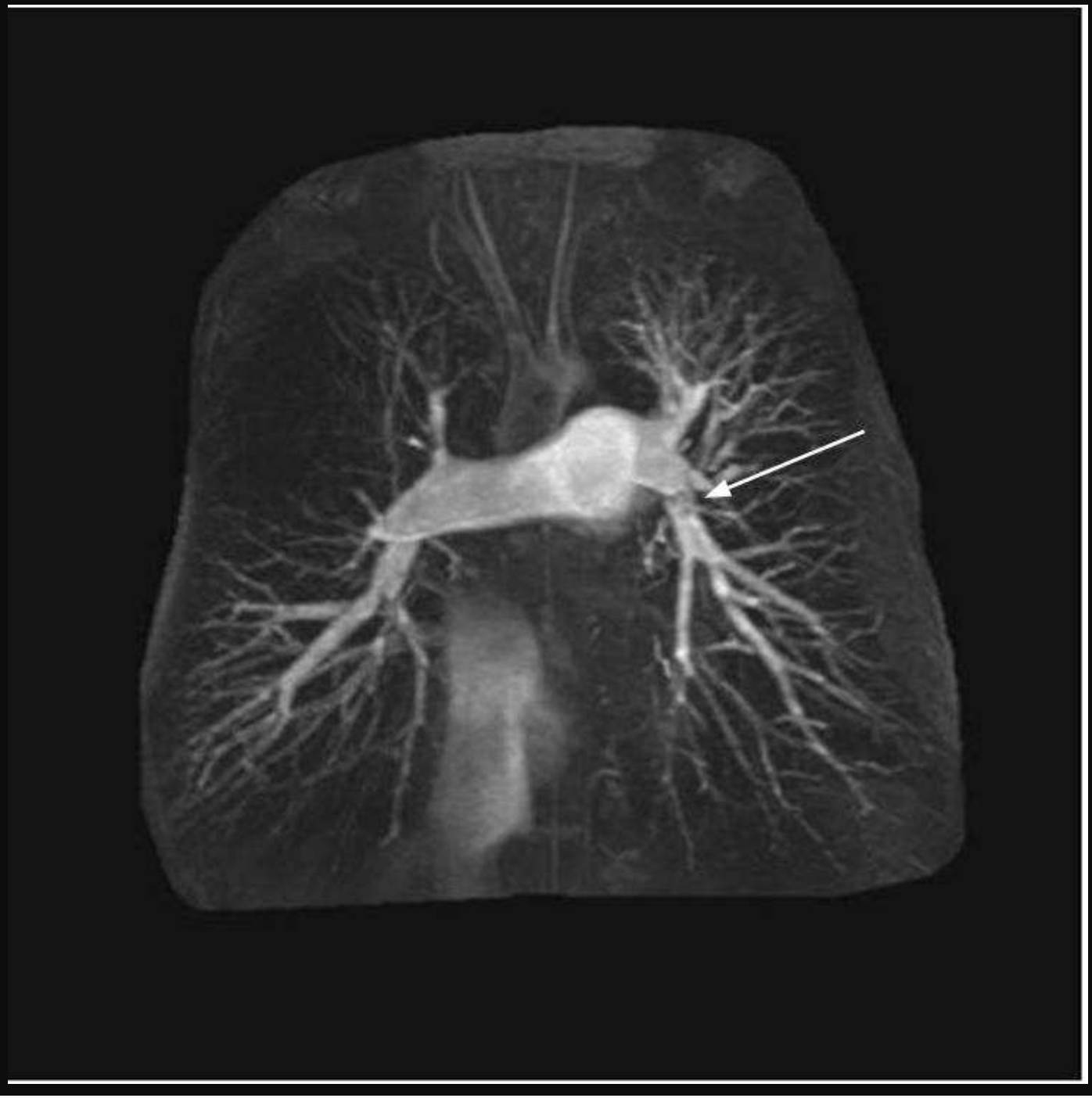
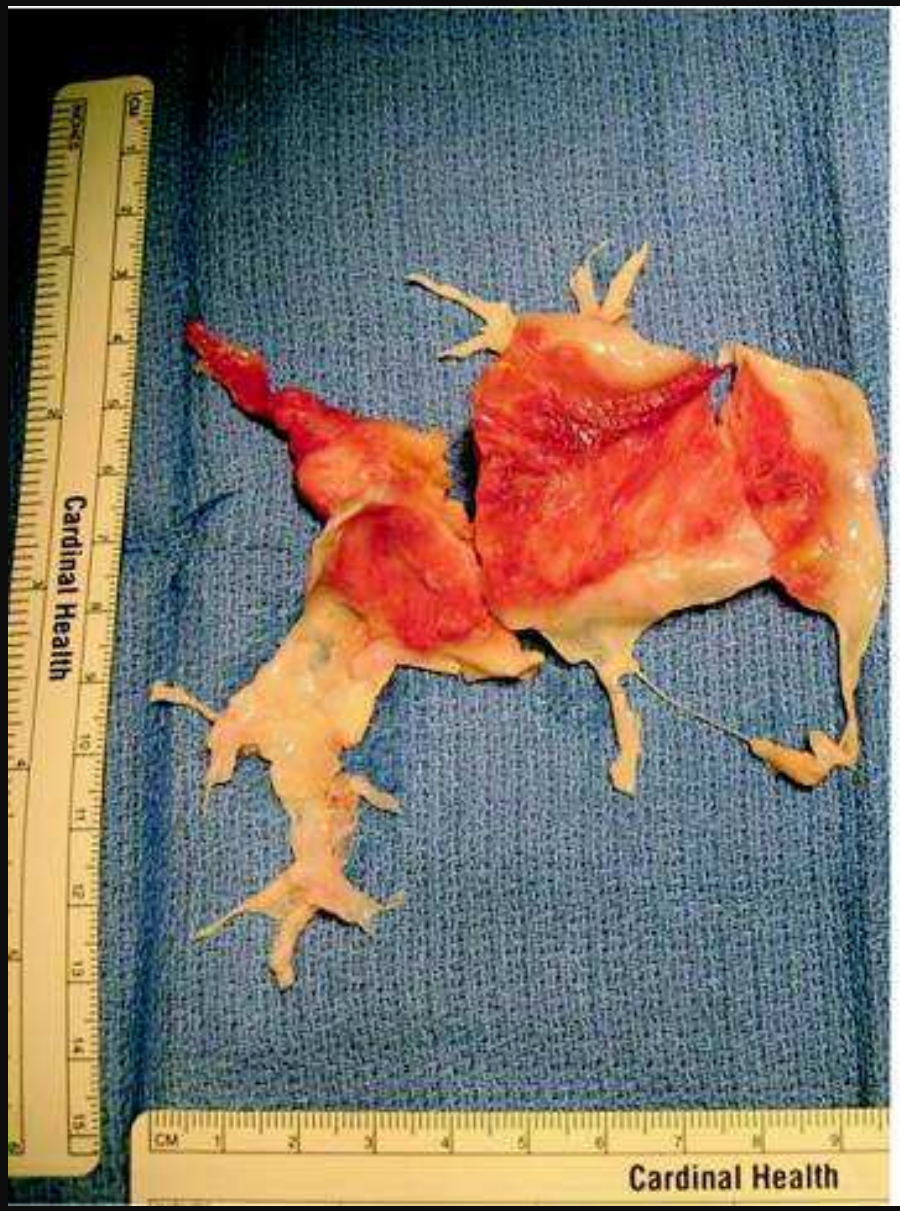
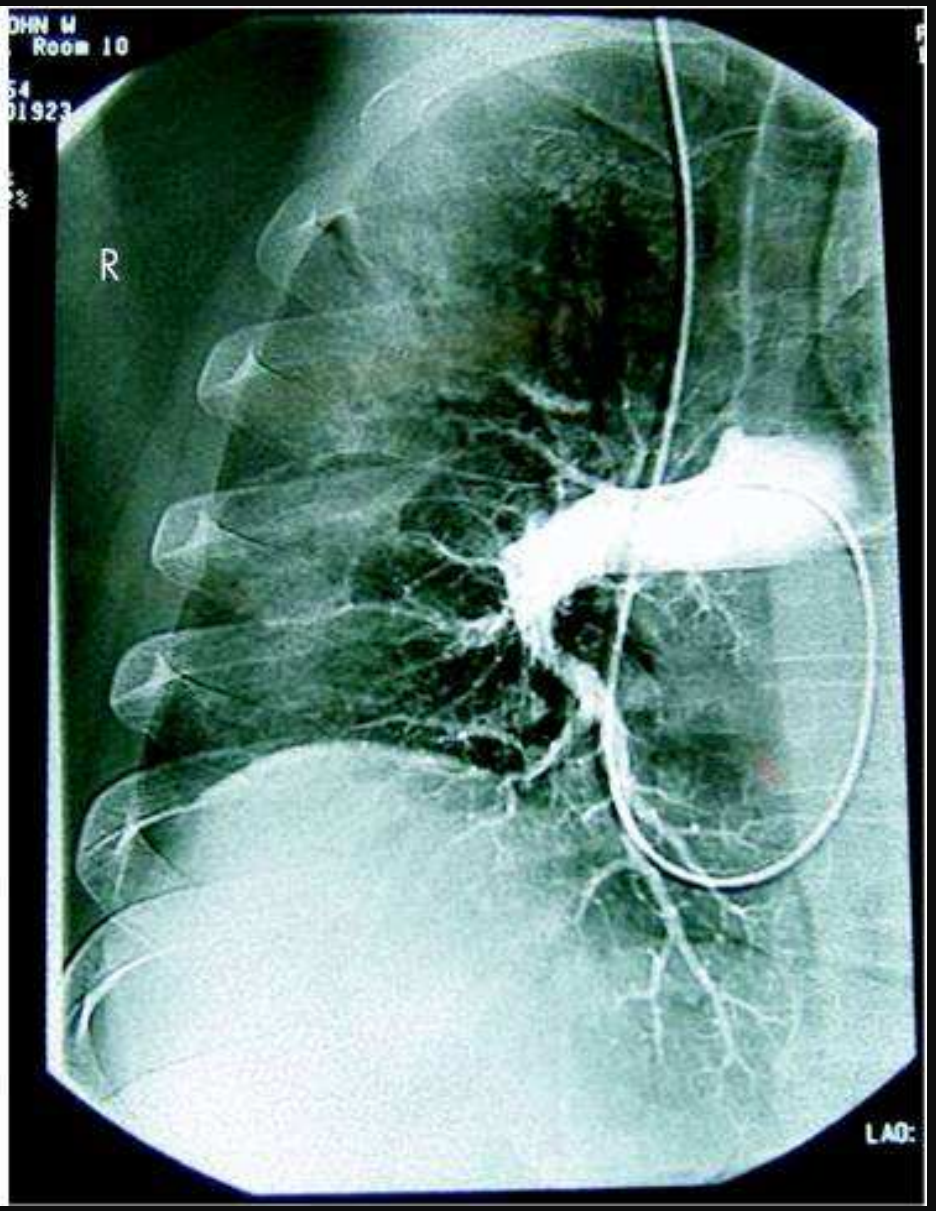


Figure 5. Schematic representation of 3 mechanisms of small-vessel disease in CTEPH. A Obstructions of small, elastic, subsegmental arteries not amenable to surgical treatment. B, Pulmonary arteriopathy in small muscular arteries and arterioles distal to unobstructed elastic vessels (medial thickening, intimal proliferation, and plexiform and colander lesions are shown). C, Pulmonary arteriopathy in small muscular arteries and arterioles distal to obstructed large elastic vessels (virtually identical changes to those in B). Reprinted from Galie et al,[71] with permission from the American Thoracic Society. Copyright 2006, American Thoracic Society.




Cardinal Health
Cardinal Health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Targeted Therapy Initiated at Diagnosis

	All Patients (n=679)	Operable Patients* (n=427)	Nonoperable Patients* (n=247)
PAH-targeted therapy, % (n)	37.9 (676)	28.3 (427)	53.8 (247)
Phosphodiesterase type V inhibitor, %	17.5	16.2	19.4
Endothelin receptor antagonist, %	21.7	12.2	37.7
Prostacyclin analogue, %	2.7	1.6	4.5
Combination therapies, %	4.0	1.6	7.7

Conclusion

- Despite similarities in clinical presentation, operable and nonoperable CTEPH patients may have distinct associated medical conditions
- Operability rates vary considerably across countries