Leids Universitair Medisch Centrum

Dutch Thrombosis Network

SAFE-SSPE study

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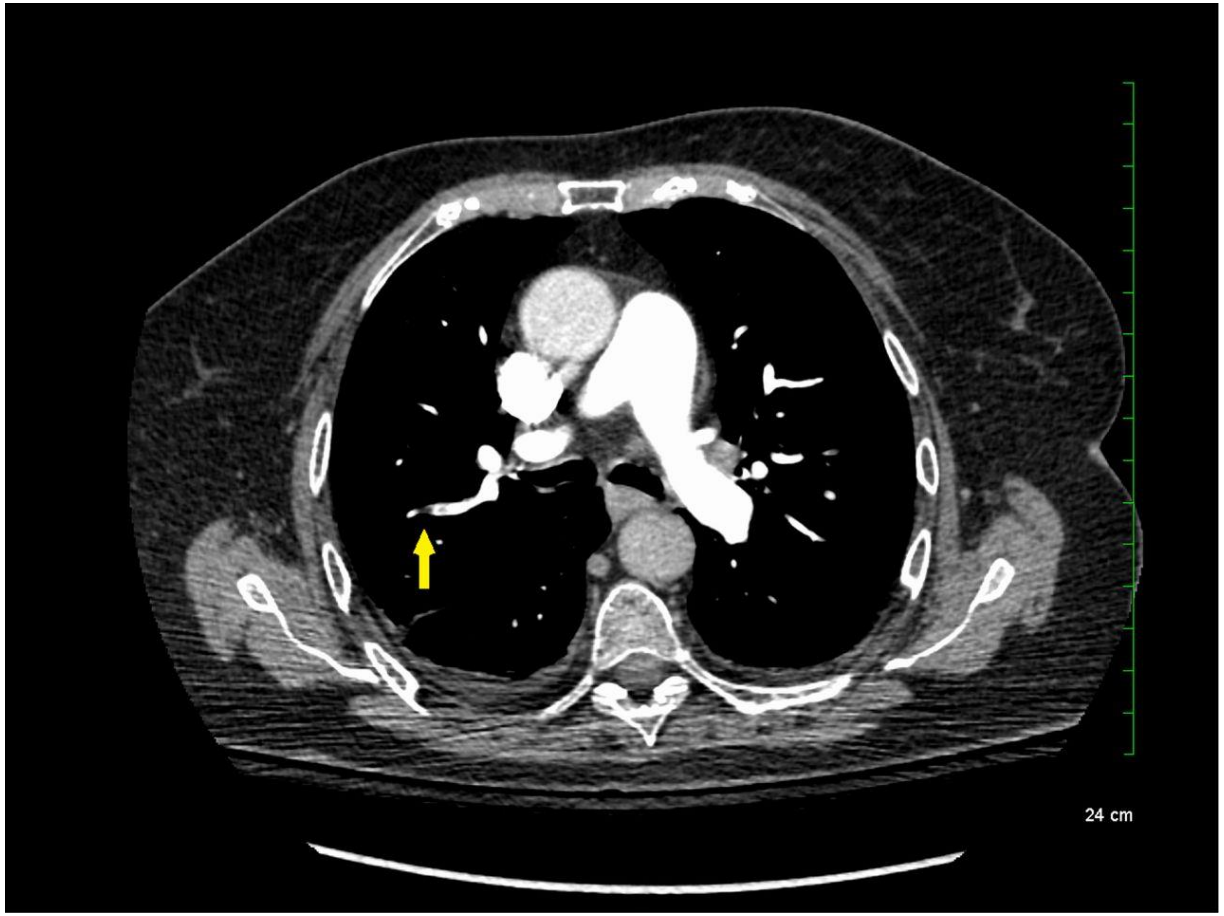
Clinical case



Definition of subsegmental PE

1. Technical quality of the scan
2. Anatomical location
3. Artery diameter

‘Natural history’ of subsegmental PE

Table 3 Rates of subsegmental pulmonary embolism diagnosis

	SDCT	All MDCT	MDCT 4 detectors	MDCT 16 detectors	MDCT 64 detectors
Number of patients	1123	1534	461	207	100
Proportion of SSPE (%, 95% CI)	4.7 (2.5–7.6)	9.4 (5.5–14.2)	7.1 (3.8–11.3)	6.9 (0.7–23.3)	15.0 (7.7–24.1)

CI, confidence intervals; MDCT, multi-detectors computed tomography; SDCT, single-detector computed tomographic pulmonary angiography; SSPE, subsegmental pulmonary embolism.

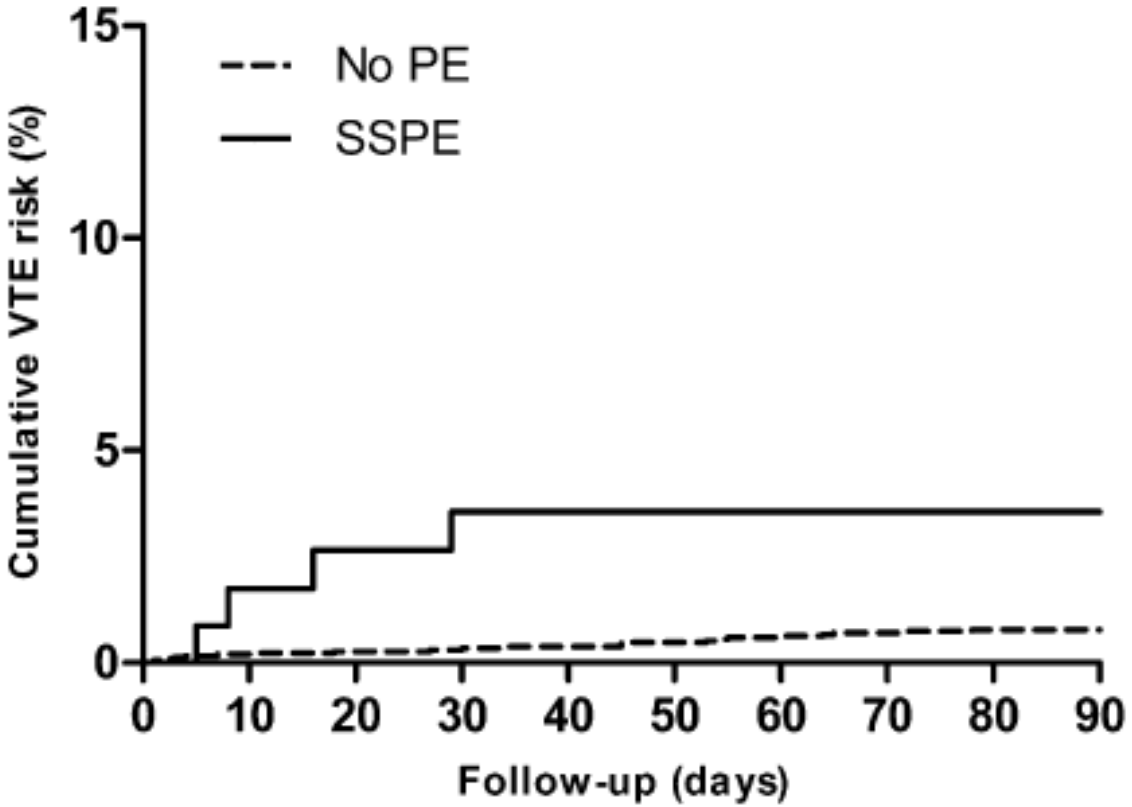
Table 4 Three-month VTE risk in patients with suspected pulmonary embolism and negative computed tomographic pulmonary angiography

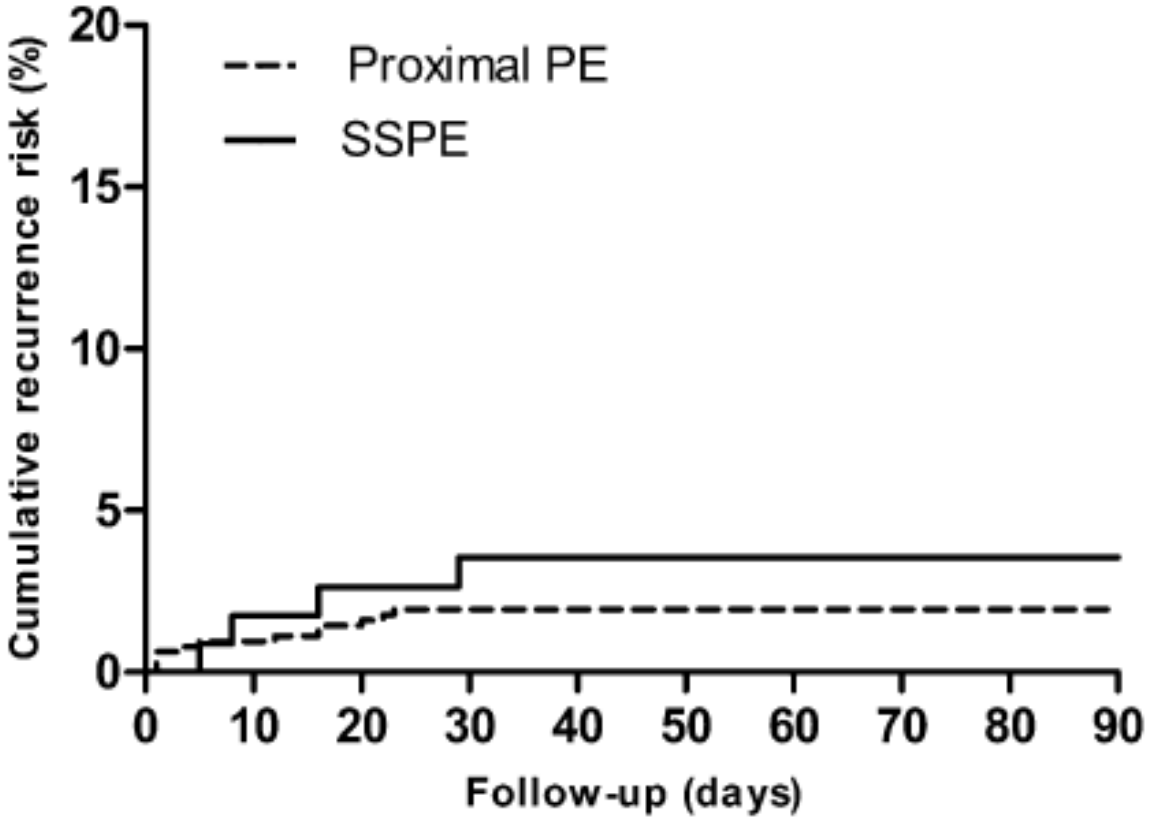
	SDCT	All MDCT	MDCT 4 detectors	MDCT 16 detectors	MDCT 64 detectors
Number of patients	1943	2982	547	424	239
Rate of VTE on follow-up (%, 95% CI)	0.9 (0.4–1.4)	1.1 (0.7–1.4)	1.4 (0.7–2.7)	0.6 (0.1–1.6)	0.8 (0.1–3.0)

CI, confidence intervals; MDCT, multi-detectors computed tomography; SDCT, single-detector computed tomographic pulmonary angiography.

Carrier M *et al*, J Thromb Haemost 2011

Prognosis of subsegmental PE





den Exter PL *et al*, Blood 2013

Treatment of subsegmental PE

5.3% (95%CI 1.6-11%)

vs.

3.9% (95%CI 4.8-13%)

Table 2. Outcomes of patients with subsegmental pulmonary embolism treated with anticoagulation

Author	N SSPE	Bleeding	VTE recurrence	Death
Aghayev	21	Unknown	Unknown	Unknown
Angriman	71	9	Unknown	Unknown
Auer	41	11	7	4
Cha	22	Unknown	6	0
Den Exter	116	2	13	12
Donato	71	5	1	0
Eyer	45	Unknown	0	0
Ghazvinian	54	Unknown	2	0
Goy	43	2	Unknown	0
Kline	54	0	1	0
Koch	9	Unknown	Unknown	Unknown
Le Gal	22	Unknown	0	Unknown
Mehta	12	[illegible]	[illegible]	0
Revel	8	[illegible]	[illegible]	0
Totals	589	31	30	16

I^2 values: VTE recurrence = 78.6% (95% CI [illegible]4.6% to [illegible]2%) and death=68[illegible] (95% CI = [illegible]5.5% to 82%)

8.1% (95%CI 2.8-16%)

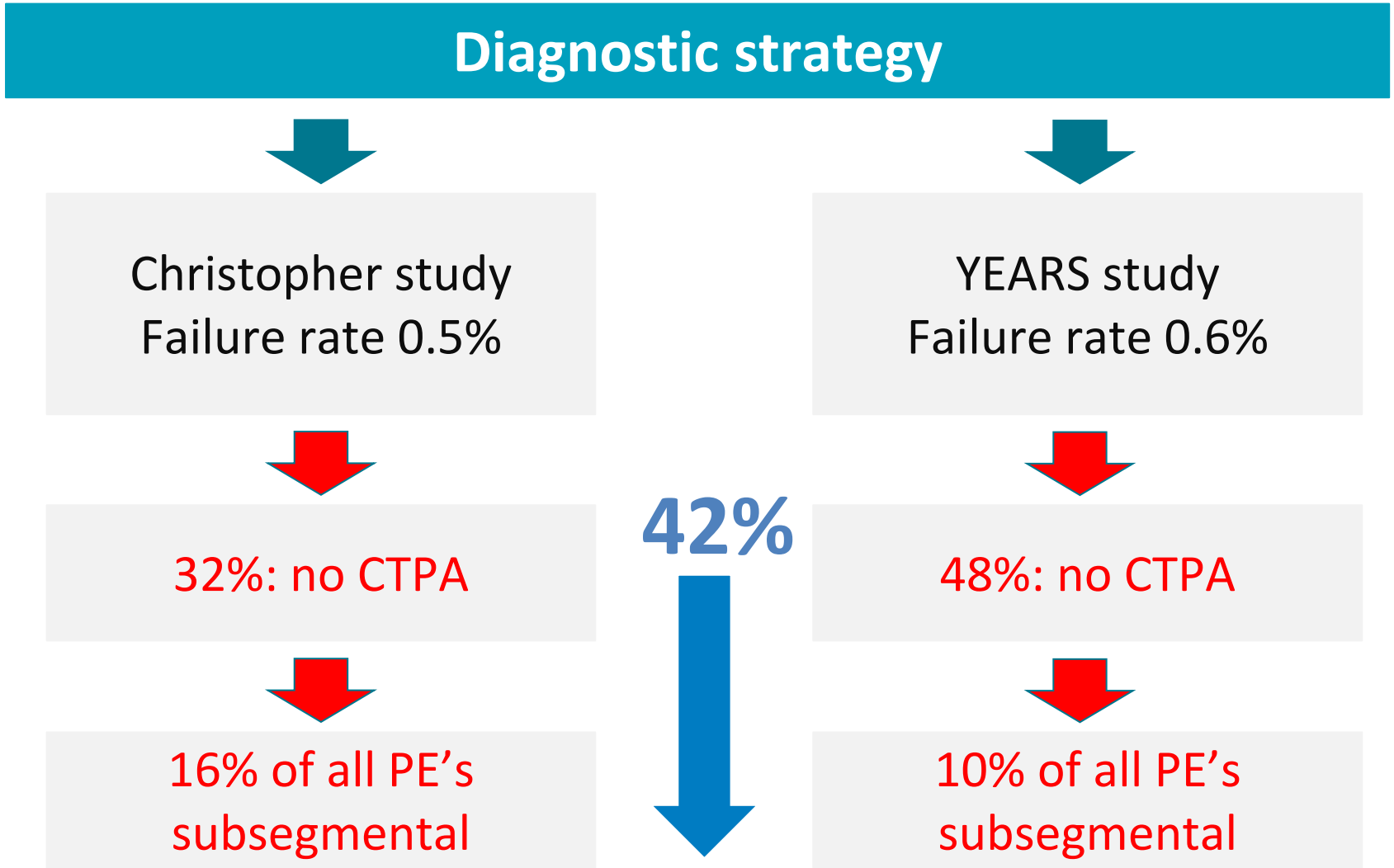
Table 3. Outc[illegible]mes of patients with subsegmental pulmonary embolism not treated with anticoagulation

Author	[illegible]N SSPE	Bleeding	VTE recurrence	Death
Angriman	8	Unknown	Unknown	Unknown
Auer	33	Unknown	7	4
Donato	22	[illegible]nknown	0	0
Eyer	32	Unkno[illegible]n	0	0
Koch	3	Unknown	Unknown	Unknown
Le Gal	8	Unknown	[illegible]	[illegible]
Mehta	20	Unknown	0	0
Totals	126	N/A	7	4

I^2 values: VTE recurrence = 71.9% (95% CI = 0% to 86.8%) and death = 42.[illegible] (95% CI [illegible]% to 77.6%)

Bariteau A *et al*, Acad Emerg Med 2018

Treatment of subsegmental PE



van Belle A *et al*, JAMA 2006; van der Hulle T *et al*, Lancet 2017; van der Pol L *et al*, Br J Haem 2018

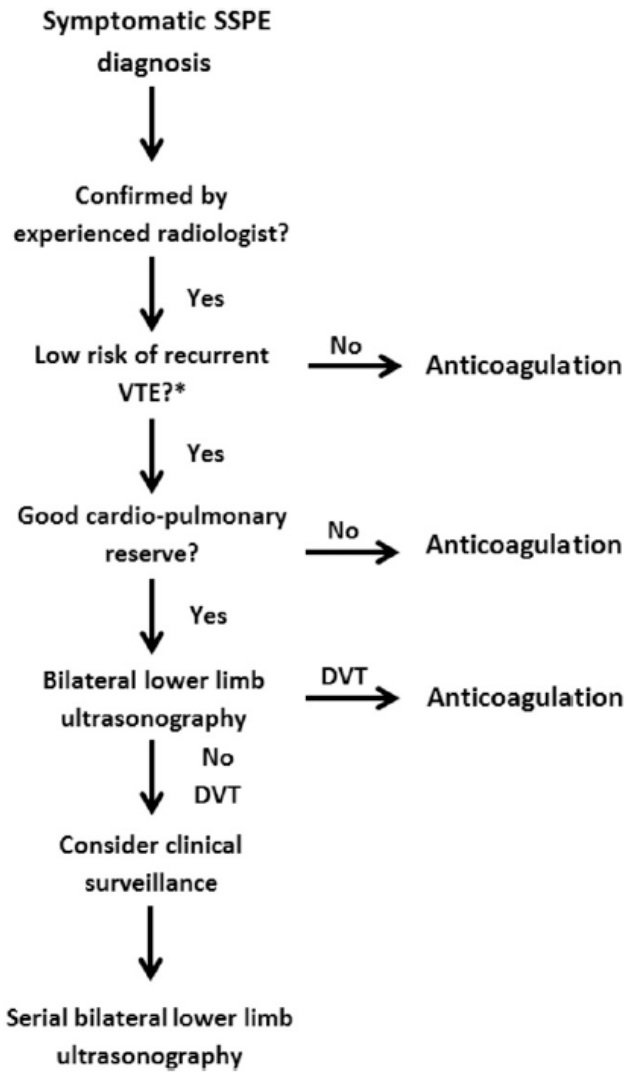
Treatment of subsegmental PE?

Whether to Anticoagulate Subsegmental PE

***19. In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation** (Grade 2C) **or (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance** (Grade 2C).

ACCP guideline 2016

Management of subsegmental PE in 2017



Carrier M and Klok FA Hematology 2017

ssPE study – cohort follow-up study

- ✓ Canada - Switzerland – Netherlands – France
- ✓ PI: Marc Carrier
- ✓ management according to guidelines: do not treat ssPE in case of ‘low-risk’ patient and serial normal bilateral CUS (day 1 and 7)
- ✓ Exclusions: Cancer; history of VTE; requirement for O2; long-term anticoagulation; pregnancy; hospitalized at time of subsegmental PE diagnosis

ssPE study – cohort follow-up study - Results

Recruitment was stopped prematurely because the predefined stopping rule was met after 292 of a projected 300 patients were enrolled

90 day primary outcome occurred in 8 patients; cumulative incidence **3.1% (95% CI, 1.6% to 6.1%)**

90 day incidence of recurrent venous thromboembolism for single subsegmental PE **2.1% (CI, 0.8% to 5.5%)** and **5.7% (CI, 2.2% to 14.4%)** for multiple subsegmental PE

No patients had fatal recurrent PE

DVT detected in 9.1 % of screened patients

Prior expectation was 1% recurrent VTE over 90 day period

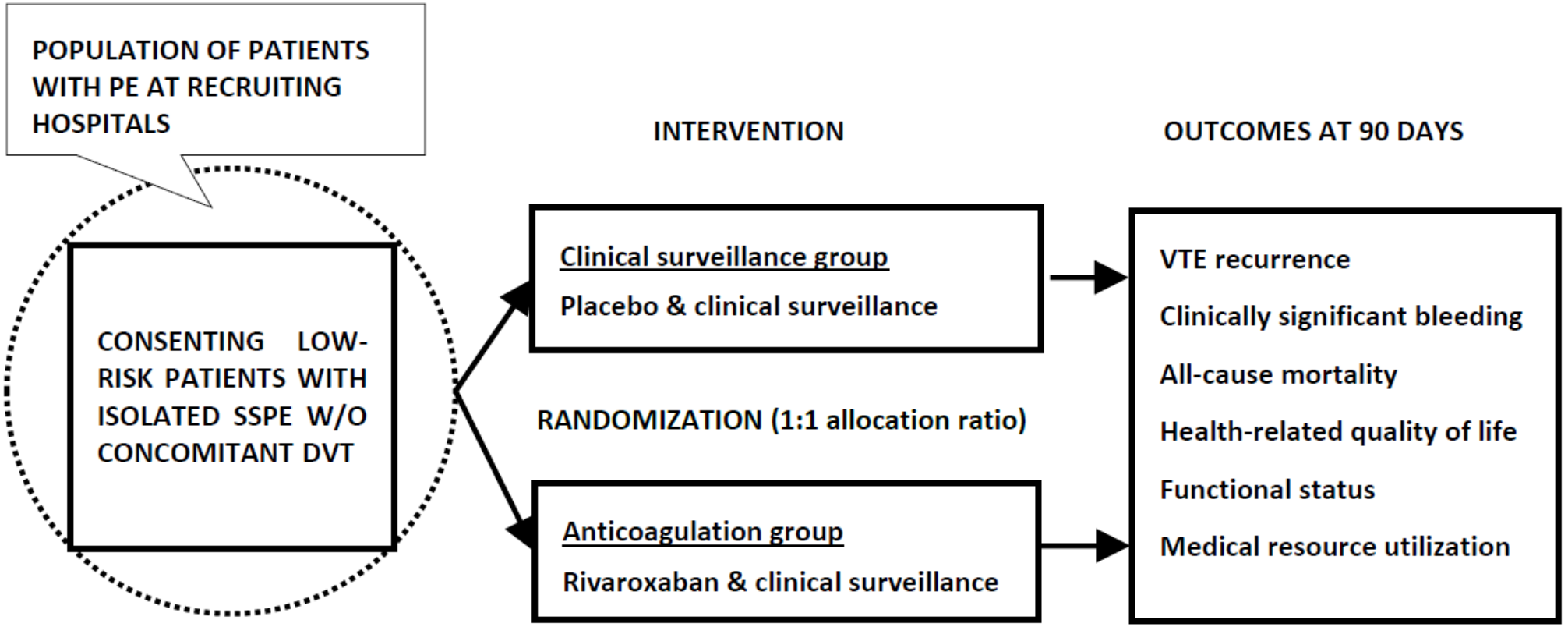
SAFE-ssPE study – protocol 2019

- ✓ Switzerland – Netherlands – Canada
- ✓ PIs: Drahomir Aujesky and Christine Baumgartner, Insel Spital Bern

SAFE-ssPE study – objective

- ✓ The overall objective is to evaluate the efficacy and safety of withholding anticoagulation in low-risk patients with isolated SSPE

SAFE-ssPE study – study flow



SAFE-ssPE study – diagnosis of PE

- ✓ Isolated SSPE is defined as multi-detector CTPA demonstrating an intraluminal filling defect in ≥1 subsegmental pulmonary artery (4th order or higher) without filling defects visualized at more proximal pulmonary artery levels.52,101,102 Isolated subsegmental defects are classified as either single (1 subsegmental vessel involved) or multiple (≥2 subsegmental vessels involved)

- ✓ The diagnosis of SSPE will be established by on-site radiologists at the time of patient presentation

SAFE-ssPE study – exclusion criteria

Presence of leg DVT or upper extremity DVT

Cancer currently treated with surgery, chemotherapy, radiotherapy, or palliative care, or during the last 6 months

≥1 prior episode of unprovoked VTE (absence of a transient or permanent risk factor)

Clinical instability (systolic blood pressure <100 mm Hg or arterial oxygen saturation <92%

Bleeding or at high risk of bleeding (e.g., ischemic stroke during preceding <10 days, major gastrointestinal bleeding during preceding <3 months, intracranial or intraocular bleeding <6 months, major trauma or surgery during preceding <1 month, platelets <75,000 per mm3, or double anti-platelet therapy at the time of enrolment

Severe renal failure (creatinine clearance <30 ml/min or severe liver insufficiency (Child-Pugh B,C)

SAFE-ssPE study – sample size

- ✓ Based on data from 127 low-risk patients with isolated SSPE who received anticoagulants (warfarin or low-molecular-weight heparin), we estimated the VTE recurrence risk in the anticoagulation group to be **0.8% at 90 days after diagnosis**

- ✓ We postulate that clinical surveillance would be non-inferior to anticoagulant treatment, specifying a **non-inferiority margin of 3.5%;** that is, that the absolute difference between the rates of recurrent VTE between the two intervention groups would not exceed 3.5%

SAFE-ssPE study – sample size

- ✓ To reach the target sample size of **276 randomized patients over a recruitment period of 43 months**, on average 3 low-risk patients with isolated SSPE need to be randomized per site and year

- ✓ Assuming that about 15% of consenting patients will be detected with concomitant DVT and will thus not be randomized, we will need to screen **about 325 patients in total**

SAFE-ssPE study – thusfar

- ✓ Total 50 patients worldwide

- ✓ In Leiden/NL: 3 patients included

Conclusion – ssPE

1. Diagnosis difficult – check with (expert) radiologist
2. In general prognosis ~ more proximal PE
3. Indirect evidence points towards category that may be left untreated, studies ongoing

Reasonable approach

Subsegmental or incidental PE?

- ✓ Check with expert radiologist
- ✓ Treat if diagnosis is confirmed
- ✓ Consider surveillance over anticoagulation if low risk subsegmental PE and no DVT (and consider participation in SAFE-SSPE study – check with Erik Klok or myself)

EXPERT-PE Conference 15-16 October 2022

Stadsgehoorzaal Leiden

- ✓ Two day conference on severe PE management Expert Conference 2022 (expert-pe.org)
- ✓ Expert talks by European colleagues
- ✓ Interactive workshops and live case presentations by ALERT teams
- ✓ Abstract submission will give reduced entry – inform with prevents.nl

European EXPERT-PE conference

Clinical case

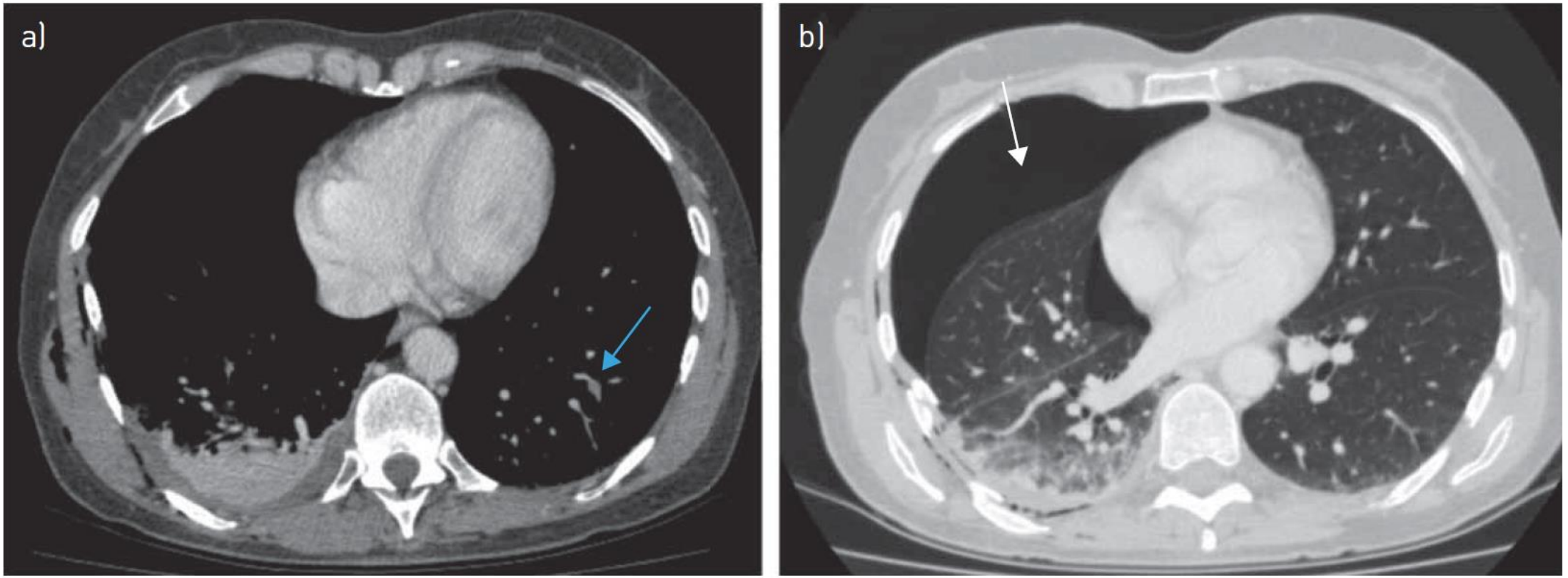


FIGURE 1 Chest computed tomography (CT) scan of patient from the clinical case. The blue arrow in panel (a) shows a filling defect in a left subsegmental pulmonary artery. Panel (b) demonstrates the pneumothorax (white arrow) and multiple costal fractures on the right side.

Conclusion

Most incidental and subsegmental pulmonary embolisms require anticoagulant treatment