

1 **Clinical presentation and outcomes in elderly patients with**
2 **symptomatic isolated subsegmental pulmonary embolism**

3

4 **Running head:** Subsegmental Pulmonary Embolism in Elderly People

5

6 **Authors:**

7 Nina Stoller, MD^a

8 Andreas Limacher, PhD, MAS, MSc^b

9 Marie Méan, MD^{a,c}

10 Christine Baumgartner, MD, MAS^a

11 Tobias Tritschler, MD^a

12 Marc Righini, MD^d

13 Jürg-Hans Beer, MD^e

14 Nicolas Rodondi, MD, MAS^{a,f}

15 Drahomir Aujesky, MD, MSc^a

16

17 **Author Affiliations:**

18 ^aDepartment of General Internal Medicine, Inselspital, Bern University Hospital,
19 University of Bern, Bern, Switzerland

20 ^bClinical Trials Unit Bern, University of Bern, Bern, Switzerland

21 ^cDivision of Internal Medicine, Lausanne University Hospital, Lausanne, Switzerland

22 ^dDivision of Angiology and Haemostasis, Geneva University Hospital, Geneva,
23 Switzerland

24 ^eDepartment of Internal Medicine, Cantonal Hospital of Baden, Baden, Switzerland

25 ^fInstitute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

26

27 **Corresponding Author:**

28 Nina Stoller, MD

29 Department of General Internal Medicine, Inselspital, Bern University Hospital

30 3010 Bern, Switzerland

31 Phone: +41 31 632 21 11

32 E-mail: nina.stoller@insel.ch

33

34 **Word count (incl. tables and legends, excl. abstract and reference list):**

35 4826 words.

36 **ABSTRACT**

37 **Objectives:** Data are limited on clinical presentation and outcomes in elderly patients
38 with acute symptomatic isolated subsegmental pulmonary embolism (SSPE). We
39 compared clinical presentation, risk factors, processes of care, and outcomes between
40 elderly patients with SSPE and patients with more proximal pulmonary embolism (PE).

41 **Methods:** We prospectively followed 578 patients aged ≥ 65 years with acute
42 symptomatic isolated SSPE or proximal PE in a multicentre Swiss cohort study. We
43 compared quality of life at three months using the PEmb-QoL, and examined the
44 independent association between localization of PE and clinical outcomes (recurrent
45 venous thromboembolism [VTE], overall mortality) using regression models with
46 adjustment for potential confounders.

47 **Results:** Overall, 11% of patients had isolated SSPE. Patients with SSPE were less
48 likely to have a pulse ≥ 110 /min (3% vs. 13%), but more likely to have active cancer
49 (28% vs. 15%) and to receive outpatient care (11% vs. 4%) than patients with proximal
50 PE. Virtually all patients (98%) with SSPE received anticoagulants. Quality of life did
51 not differ between the groups at 3 months. No patient with SSPE vs. seven patients
52 with proximal PE died from the index PE event. No significant difference was observed
53 for the 3-year cumulative incidence of recurrent VTE (7% vs. 12%) and death (29% vs.
54 20%). After adjustment, SSPE was not associated with a lower risk of clinical outcomes
55 than proximal PE.

56 **Conclusions:** Clinical presentation and incidences of adverse outcomes did not differ
57 significantly between elderly patients with SSPE or proximal PE, although the power
58 to detect differences might have been limited given the small number of events. Thus,
59 our study does not provide evidence that unselected, elderly patients with SSPE have
60 a more benign clinical course.

61 **Keywords:** Aged; Anticoagulants; Patient outcome assessment; Pulmonary
62 embolism; Venous thromboembolism

63

64 **Abbreviations:**

65	AC	Anticoagulation
66	BP	Blood pressure
67	CI	Confidence interval
68	CT(PA)	Computed tomography (pulmonary angiography)
69	DOAC	Direct oral anticoagulant
70	DVT	Deep vein thrombosis
71	Hs-cTNT	High-sensitivity cardiac troponin T
72	INR	International Normalized Ratio
73	IQR	Interquartile range
74	NSAID	Non-steroidal anti-inflammatory drugs
75	PEmb-QoL	Pulmonary Embolism Quality of Life
76	PESI	Pulmonary Embolism Severity Index
77	(S)HR	(Sub-)hazard ratios
78	(SS)PE	(Subsegmental) pulmonary embolism
79	SWITCO65+	Swiss cohort of elderly patients with venous thromboembolism
80	VKA	Vitamin K antagonist
81	VTE	Venous thromboembolism

82 INTRODUCTION

83 Acute isolated subsegmental pulmonary embolism (SSPE), defined as
84 pulmonary embolism (PE) that occurs in one or more subsegmental pulmonary artery
85 branches but no larger order of vessels [1], is increasingly detected with the
86 technological advance in computed tomography pulmonary angiography (CTPA) [2].
87 SSPE represents 7–36% of cases of PE [3-6], and the vast majority of patients with
88 SSPE receive anticoagulant treatment [6]. However, the diagnosis and treatment of
89 SSPE pose several challenges. Given a positive predictive value of as low as 25% for
90 SSPE with CTPA and an only fair interobserver agreement between radiologists [7, 8],
91 many cases of SSPE may represent false-positive results (e.g., artefacts) rather than
92 true PE [9]. It has also been hypothesized that the lung may act as a natural filter to
93 protect systemic circulation and therefore, SSPE may represent a normal finding [10].
94 Moreover, direct and indirect evidence from retro- and prospective studies suggests
95 that SSPE may have a less severe clinical presentation and a lower risk of venous
96 thromboembolism (VTE) recurrence and PE-related death than more proximal PE [3,
97 4, 11], and that withholding anticoagulation in selected low-risk patients with SSPE
98 (i.e., those without concomitant proximal deep vein thrombosis [DVT]) could be safe
99 [4, 12, 13]. In contrast, another study found that patients with SSPE mimic those with
100 more proximal PE in regard to their risk profile and clinical outcomes [5].

101 Although the majority of VTE cases occur in patients aged ≥ 65 years [14], little
102 is known about the clinical presentation, VTE risk factors, processes of care, and
103 outcomes in elderly patients with isolated SSPE. Previous studies on SSPE were
104 mostly performed in patients aged < 70 years [12], and whether their results can be
105 generalized to the elderly remains unknown. To fill this gap of knowledge, we
106 compared the clinical presentation, VTE risk factors, processes of care, and outcomes
107 between elderly patients with isolated SSPE and those with more proximal PE. Given

108 the diagnostic uncertainty and doubtful clinical relevance of SSPE, we hypothesized
109 that elderly patients with SSPE are less likely to experience adverse outcomes
110 compared to patients with more proximal PE.

111 **METHODS**

112 **Cohort sample**

113 The study was conducted as part of the Swiss cohort of elderly patients with
114 VTE (SWITCO65+) [15]. In this multicentre prospective cohort study, consecutive in-
115 and outpatients aged ≥ 65 years with acute symptomatic, objectively confirmed VTE
116 were enrolled at nine Swiss hospitals between September 2009 and March 2012 and
117 followed until December 2013. Exclusion criteria comprised the inability to provide
118 informed consent (i.e., severe dementia), impracticable follow-up due to terminal
119 illness or place of living too far away from the study centre, insufficient German or
120 French speaking ability, venous thromboses other than lower limb DVT or PE (e.g.,
121 catheter-related thrombosis), or prior enrolment in the cohort. The detailed study
122 methods, including eligibility criteria, were published previously [15]. The study was
123 approved by the ethics committees at each participating site.

124 For the present study, we considered all patients from the original cohort who
125 had an initial diagnosis of symptomatic PE (i.e., acute chest pain, new or worsening
126 dyspnoea, or syncope) detected by an objective imaging exam, such as spiral CTPA,
127 pulmonary angiography, or high-probability ventilation/perfusion scintigraphy [15].
128 Patients who had a diagnosis of SSPE without the presence of any more proximal PEs
129 based on the interpretation of on-site radiologists were considered to have isolated
130 SSPE. Because proximal DVT is associated with adverse outcomes in patients with
131 PE [16], we excluded patients with isolated SSPE who had concomitant proximal DVT.

132

133 **Data collection**

134 For all enrolled patients, trained study nurses prospectively collected
135 information about baseline demographics such as age, sex, localization of the index
136 PE (SSPE vs. more proximal PE), VTE risk factors (active cancer, immobilisation,

137 major surgery, oestrogen therapy, and history of VTE), comorbidities (chronic heart
138 failure, chronic lung disease, and history of major bleeding), clinical symptoms and
139 signs of VTE (acute chest pain, new or worsening dyspnoea, new unilateral leg pain
140 or leg swelling, pulse, systolic blood pressure, respiratory rate, body temperature,
141 mental status, arterial oxygen saturation), and routine laboratory findings
142 (haemoglobin, platelet count). The revised Geneva score as a clinical decision rule to
143 assess the risk of PE in patients with suspected PE and the Pulmonary Embolism
144 Severity Index (PESI) to estimate the 30-day overall mortality risk were calculated
145 retrospectively [17, 18]. We further assessed the therapy initiated within one month of
146 the index PE (vitamin K antagonists [VKA], parenteral anticoagulation, no
147 anticoagulation, thrombolysis, inferior vena cava filter), concomitant treatments
148 (antiplatelet and non-steroidal anti-inflammatory drugs), and the initial site of
149 management (in- or outpatient setting). Type and duration of anticoagulation as well
150 as the site of initial management was left to the discretion of the managing physicians.

151

152 **Study outcomes**

153 The primary outcome was the recurrence of symptomatic VTE during the follow-
154 up period, defined as a new or recurrent, fatal or non-fatal, symptomatic, and
155 objectively confirmed PE and/or DVT, as previously described [15]. Secondary
156 outcomes included overall mortality, PE-related mortality (defined as deaths certainly
157 or possibly related to PE), and PE-specific quality of life based on the Pulmonary
158 Embolism Quality of Life (PEmb-QoL) questionnaire. The PEmb-QoL questionnaire is
159 an instrument with six dimensions (frequency of complaints, limitations in activities of
160 daily living, work-related problems, social limitations, intensity of complaints, and
161 emotional complaints) and 40 items to measure quality of life in patients with PE
162 reflecting the patients' perspective over the past four weeks [19, 20]. The summary

163 score ranges between zero (best quality of life) and 100 (worst quality of life) [21, 22]
164 with an assumed minimal clinically important difference of 15 points [23]. We used the
165 validated French and German versions of the PEmb-QoL [21, 22]. The tertiary outcome
166 was the duration and quality of oral anticoagulation with VKAs, the latter expressed as
167 the percentage of time spent in a given International Normalized Ratio [INR] range
168 (<2.0, 2.0–3.0, >3.0) according to Rosendaal's method [24]. Patients who did not take
169 VKA, had less than two INR measurements, or died within the first six months, were
170 excluded from analyses of anticoagulation.

171 Follow-up included one telephone interview and two face-to-face evaluations
172 during the first year of study participation and then semi-annual contacts, alternating
173 between face-to-face evaluations and telephone calls, as well as periodic hospital chart
174 reviews. As part of the follow-up interviews/visits, study nurses obtained information
175 about the date and localization of VTE recurrence, death, and PE-specific quality of
176 life. We also collected INR values throughout follow-up. A committee of 3 independent,
177 blinded clinical experts adjudicated all outcomes. They classified the cause of all
178 deaths as definitely due to PE (i.e., confirmed by autopsy or death following a clinically
179 severe PE), possibly related to PE (i.e., death in a patient who died suddenly without
180 any other explanation), or due to another cause. PE-related death was defined as
181 death definitely or possibly related to recurrent PE. Final assignments were based on
182 the full consensus of this committee.

183

184 **Statistical analyses**

185 We compared baseline characteristics, mean PEmb-QoL summary scores at
186 three months, duration of anticoagulation, and the percentage of time spent in a given
187 INR range (<2.0, 2.0–3.0, >3.0) between patients with isolated SSPE and those with
188 more proximal PE using chi-square or Wilcoxon rank-sum tests as appropriate. A P-

189 value <0.05 was considered statistically significant. Recurrent VTE, overall mortality,
190 and PE-related mortality in patients with SSPE vs. those with more proximal PE were
191 compared at three months and over the entire follow-up period. We additionally
192 compared PE-related deaths that occurred during the index hospitalization to assess
193 mortality due to the index PE. The 3-year cumulative incidences of recurrent VTE
194 events by localization of PE were compared using the Aalen-Johansen estimator and
195 the Gray test, which both account for the competing risk of death [25, 26]. For mortality,
196 we used the Kaplan-Meier estimator and the log-rank test.

197 We explored the associations between SSPE and the time to a first recurrent
198 VTE using competing risk regression [27], accounting for non-PE-related death as a
199 competing event. The method yields sub-hazard ratios (SHR) with corresponding 95%
200 confidence intervals (CIs). We adjusted the models for risk factors previously shown to
201 be associated with recurrent VTE (age, sex, active cancer, history of VTE) [28-32], as
202 well as periods of anticoagulation as a time-varying covariate. For overall mortality, we
203 used Cox-regression with robust standard errors, adjusting for age, sex, active cancer,
204 chronic lung disease, heart failure [18, 33, 34], and periods of anticoagulation as a
205 time-varying covariate. Because the diagnosis of SSPE based on ventilation/perfusion
206 scanning is not standardized, we excluded all non-CTPA-based PE cases in a
207 sensitivity analysis. We assumed missing values in adjustment variables to be normal
208 or absent as done previously [18, 35]. All analyses were done using Stata 15 (Stata
209 Corporation, College Station, Texas).

210 **RESULTS**

211 **Study sample**

212 Of 1863 screened patients with symptomatic VTE, we excluded 462 who had
213 ≥ 1 exclusion criterion and 398 who did not consent to participate (Fig. 1). After the
214 exclusion of another 425 patients who withdrew from the study within one day of
215 enrolment, refused the use of their data, had objectively confirmed DVT only, or had
216 concomitant proximal DVT, our final sample comprised 578 patients. Of these, 64 had
217 isolated SSPE (11%) and 514 more proximal PE.

218 The median age was 75 years (interquartile range [IQR] 70–81 years) and 53%
219 of patients were men. Patients with isolated SSPE were more likely to have active
220 cancer (28% vs. 15%, $P=0.01$) and less often to have a pulse $\geq 110/\text{min}$. (3% vs. 13%,
221 $P=0.02$) than patients with proximal PE (Table 1). The revised Geneva score, cardiac
222 biomarker levels, and the short-term mortality risk based on the PESI were comparable
223 between the two groups.

224 All but four patients (1 with isolated SSPE, 3 with more proximal PE) were
225 treated with initial anticoagulants (VKA or parenteral anticoagulation), but the initiation
226 of VKA therapy was less frequent in patients with isolated SSPE than in patients with
227 more proximal PE (80% vs. 91%, $P=0.01$; Table 1). Patients with isolated SSPE were
228 more often treated as outpatients (11% vs. 4%, $P=0.02$). The median follow-up period
229 was 30 months (IQR 18–36 months).

230

231 **Primary outcome (recurrence of VTE)**

232 The risk of recurrent VTE at three months and over the entire follow-up period
233 (Table 2), and the 3-year cumulative incidence of recurrent VTE (Fig. 2a) did not differ
234 significantly between patients with SSPE and those with more proximal PE. After
235 adjustment, there was no statistically significant difference in recurrent VTE during

236 follow-up between the two groups (SHR 0.64, 95%CI: 0.25–1.62; Table 3). Excluding
237 the 58 patients in whom PE-diagnosis was not based on CTPA in a sensitivity analysis
238 did not substantially change the results (SHR 0.57, 95%CI: 0.20–1.62; Table 3).

239

240 **Secondary outcomes (overall mortality, PE-related mortality, PE-specific** 241 **quality of life)**

242 Of the 18 patients with isolated SSPE who died during follow-up, two died from
243 possible recurrent PE (sudden death without any other explanation) on day 82 and
244 1120 of follow-up. Of the 97 patients with proximal PE who died during follow-up, 21
245 patients died from definite (n=6) or possible PE (n=15). Of these, seven died from PE
246 during the hospitalization for index PE. Overall mortality and mortality definitely or
247 possibly related to PE during the index hospitalization, at three months, and over the
248 entire follow-up period (Table 2), as well as the 3-year cumulative incidence of overall
249 mortality (Fig. 2b), did not differ significantly between patients with isolated SSPE and
250 those with more proximal PE. After adjustment, the risk of overall mortality did not differ
251 between the two groups (hazard ratio [HR] 1.12, 95%CI: 0.64–1.96; Table 3). After the
252 exclusion of the 58 patients without a CTPA-based PE diagnosis, mortality did not differ
253 by PE localization (HR 1.34, 95%CI: 0.71–2.53, Table 3).

254 PE-specific quality of life, expressed as the PEmb-QoL summary score at three
255 months following the index PE, was similar in patients with isolated SSPE and those
256 with more proximal PE (median 22.8 vs. 22.9 points; P=0.70).

257

258 **Tertiary outcomes (duration and quality of anticoagulation)**

259 The median duration of initial anticoagulation did not differ between patients with
260 SSPE and those with more proximal PE (10.7 [IQR 6.1–24.1] vs. 12.3 [6.3–28.7])

261 months; $P=0.34$; Table 4). The quality of anticoagulation, expressed as the time in a
262 given INR range, was also comparable between the PE groups (Table 5).

263 **DISCUSSION**

264 In our prospective study of elderly patients with acute symptomatic PE, patients
265 with isolated SSPE did not differ significantly in their clinical presentation, but had a
266 higher prevalence of cancer, and a higher probability of receiving outpatient treatment
267 than patients with more proximal PE. The PESI risk classes, the duration and quality
268 of anticoagulation, and short- and long-term clinical outcomes did not differ significantly
269 between the two groups, although the power to detect differences might have been
270 limited given the small number of events. To our knowledge, this is the first study
271 exploring differences between SSPE and proximal PE in the elderly.

272 Whether isolated SSPE is clinically more benign than more proximal PE remains
273 controversial. Studies of younger patients demonstrated that patients with isolated
274 SSPE have a lower prevalence of new/worsening dyspnoea and concomitant DVT [3,
275 36], lower levels of biomarkers, fewer signs of right-ventricular dysfunction [3], and a
276 lower prevalence of arterial hypoxemia and tachycardia than patients with more
277 proximal PE [3, 37]. Our results could not show that elderly patients with isolated SSPE
278 have a more subtle clinical presentation.

279 Elderly patients with isolated SSPE and more proximal PE did not differ in terms
280 of VTE risk factors and comorbid conditions in our study, with the exception of a higher
281 cancer prevalence in the SSPE group (28% vs. 15%). The latter may be potentially
282 explained by a lower threshold to perform CTPA in elderly patients with active cancer,
283 thus increasing the rate of detected oligosymptomatic SSPE. Alternatively, the
284 prothrombotic state associated with cancer could result in a greater risk for small,
285 peripheral PE in the elderly.

286 Our finding that the vast majority of patients with isolated SSPE are managed
287 with anticoagulation treatment is consistent with the results from surveys and other
288 studies [6, 38, 39]. We did not observe a statistically significant difference in the

289 duration of initial anticoagulation in patients with SSPE and more proximal PE,
290 demonstrating that physicians do not primarily use the localization of PE to determine
291 the duration of anticoagulant treatment. The higher proportion of outpatient
292 management in patients with SSPE compared with proximal PE (11% vs. 4%) indicates
293 that physicians perceive the risk of adverse outcomes related to SSPE to be lower.
294 The lower proportion of VKA treatment in patients with SSPE is most probably
295 attributable to the higher prevalence of cancer in this group.

296 We did not find statistically significant differences in recurrent VTE, overall
297 mortality, PE-related mortality, and PE-specific quality of life between patients with
298 isolated SSPE and proximal PE, acknowledging that the number of outcome events
299 was low in our study. The slightly higher 3-year cumulative mortality incidence in
300 patients with SSPE (29% vs. 20%) could be explained with the higher prevalence of
301 cancer in this group. After adjustment for potential confounders, isolated SSPE was
302 not independently associated with a lower risk of clinical outcomes compared to
303 proximal PE. Our results are consistent with a study by den Exter, et al., who did not
304 find statistically significant differences in the 3-month risks of recurrent VTE and overall
305 mortality between anticoagulated patients with isolated SSPE and more proximal PE,
306 although the age of their study population was lower (mean age 56 years) [5]. However,
307 as almost all patients received anticoagulation in our and den Exter's study, outcome
308 comparisons between SSPE vs. proximal PE may be blurred. Interestingly, seven
309 deaths were related to the index PE in the proximal PE group vs. zero in the SSPE
310 group. This finding indicates that case-fatality may not be a direct consequence of
311 SSPE, which is unlikely to cause hemodynamic instability.

312 A growing body of evidence from retrospective and non-randomized prospective
313 studies suggests that withholding anticoagulation may be as safe as anticoagulant
314 treatment in selected low-risk patients with isolated SSPE [12, 13]. Our study does not

315 provide any evidence that isolated SSPE represents a clinically more benign form of
316 PE in the elderly. However, a substantial proportion of patients in our sample had
317 cancer (28%) or concomitant DVT (3%), two well-known risk factors for recurrent VTE
318 [28, 31, 32], and death [16, 18, 33, 34]. Thus, withholding anticoagulation in selected
319 low-risk patients with isolated SSPE, i.e., those without cancer or concomitant DVT,
320 may still be an option but the risk-benefit ratio of such an approach should be examined
321 in a randomized trial before it can be adopted into clinical practice.

322 Our study has potential limitations. First, as patients were solely enrolled in
323 hospital in- and outpatient services, healthier patients with clinically more benign forms
324 of SSPE who were diagnosed and entirely managed outside the hospital may be
325 underrepresented in our study. Second, as in most studies of SSPE, the diagnosis of
326 isolated SSPE was made by on-site radiologists and was not independently
327 adjudicated [5, 40, 41]. Because the interobserver agreement for SSPE based on
328 CTPA is only fair ($k=0.38$) [8] and the diagnosis of SSPE based on ventilation/perfusion
329 scanning is not standardized [42], we cannot exclude the possibility that some patients
330 were misclassified as having isolated SSPE in our study. However, when we
331 considered only CTPA-based PEs in a sensitivity analysis, the results did not change
332 markedly, confirming the robustness of our findings. Third, we could not distinguish
333 isolated single from multiple SSPEs, as the number of SSPEs were not documented
334 in our database. As no studies comparing the prognosis of single vs. multiple isolated
335 SSPEs exist, whether patients with single vs. multiple SSPE have differential
336 outcomes, is unknown. Fourth, the assessment of concomitant DVT was not
337 systematic but was left to the discretion of the managing physicians, which must have
338 resulted in an underestimation of the true prevalence of concomitant DVT. Fifth, this
339 study is an ancillary study from the SWITCO65+ cohort and we have not done a power
340 calculation. Thus, the relatively small number of events limits the power to detect

341 potential outcome differences between SSPE and more proximal PE. Finally, direct
342 oral anticoagulants (DOACs) were not authorized for treatment of acute VTE during
343 the study recruitment period in Switzerland and it is possible that bleeding rates would
344 be lower if DOACs rather than VKAs had been used [43].

345 In conclusion, clinical presentations and incidences of adverse outcomes did
346 not differ significantly between elderly patients with SSPE and those with proximal PE,
347 although the power to detect differences might have been limited given the small
348 number of events. Overall, our study does not provide any evidence that unselected,
349 elderly patients with isolated SSPE have a benign clinical course and may not need
350 anticoagulant treatment. Whether withholding anticoagulation in selected low-risk
351 patients with isolated SSPE (e.g., those without cancer or concomitant DVT) is safe,
352 must be examined in a future randomized-controlled trial.

353

354 **ADDENDUM**

355 **Authorship**

356 N. Stoller, A. Limacher, and D. Aujesky were responsible for study design. A. Limacher
357 did the statistical analyses. N. Stoller and D. Aujesky wrote the manuscript. A.
358 Limacher, M. Méan, C. Baumgartner, T. Tritschler, M. Righini, JH. Beer, and N.
359 Rodondi critically reviewed the manuscript. M. Méan, M. Righini, JH. Beer, N. Rodondi,
360 and D. Aujesky collected data and obtained funding from the Swiss National Science
361 Foundation. All authors had full access to the data and a role in the writing of this
362 manuscript.

363

364 **Declaration of competing interest**

365 N. Stoller, A. Limacher, M. Méan, C. Baumgartner, M. Righini, N. Rodondi, and D.
366 Aujesky have nothing to disclose. T. Tritschler reports grants from the Swiss National
367 Science Foundation (SNF P2ZHP3_177999), and non-financial support from Pfizer,
368 outside the submitted work. JH. Beer has received research grant support from the
369 Swiss National Science Foundation and from the Swiss Heart Foundation, grant
370 support, lecture and conference fees from Böhringer, Pfizer, Bayer, and Daiichi Sankyo
371 Company. We have no writing assistance to declare.

372

373 **FUNDING**

374 This study was supported by the Swiss National Science Foundation [33CSCO-
375 122659/139470]. The sponsor had no role in study design, data collection, site
376 monitoring, data analysis, data interpretation, or writing of the manuscript.

377

378 **ACKNOWLEDGEMENTS**

379 The authors thank all collaborators of the SWITCO65+ study.

380 **REFERENCE LIST**

- 381 1. Stein PD, Goodman LR, Hull RD, Dalen JE, Matta F. Diagnosis and management of
382 isolated subsegmental pulmonary embolism: review and assessment of the options. *Clin*
383 *Appl Thromb Hemost*. 2012;**18**:20-6. doi: 10.1177/1076029611422363.
- 384 2. Carrier M, Righini M, Wells PS, et al. Subsegmental pulmonary embolism diagnosed
385 by computed tomography: incidence and clinical implications. A systematic review and meta-
386 analysis of the management outcome studies. *Journal of thrombosis and haemostasis : JTH*.
387 2010;**8**:1716-22. doi: 10.1111/j.1538-7836.2010.03938.x.
- 388 3. Cha SI, Shin KM, Lee JW, et al. Clinical characteristics of patients with peripheral
389 pulmonary embolism. *Respiration*. 2010;**80**:500-8. doi: 10.1159/000277929.
- 390 4. Donato AA, Khoche S, Santora J, Wagner B. Clinical outcomes in patients with
391 isolated subsegmental pulmonary emboli diagnosed by multidetector CT pulmonary
392 angiography. *Thrombosis research*. 2010;**126**:e266-70. doi: 10.1016/j.thromres.2010.07.001.
- 393 5. den Exter PL, van Es J, Klok FA, et al. Risk profile and clinical outcome of
394 symptomatic subsegmental acute pulmonary embolism. *Blood*. 2013;**122**:1144-9. doi:
395 10.1182/blood-2013-04-497545.
- 396 6. Raslan IA, Chong J, Gallix B, Lee TC, McDonald EG. Rates of Overtreatment and
397 Treatment-Related Adverse Effects Among Patients With Subsegmental Pulmonary
398 Embolism. *JAMA internal medicine*. 2018;**178**:1272–4. doi:
399 10.1001/jamainternmed.2018.2971.
- 400 7. Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for
401 acute pulmonary embolism. *The New England journal of medicine*. 2006;**354**:2317-27. doi:
402 10.1056/NEJMoa052367.
- 403 8. Ghanima W, Nielssen BE, Holmen LO, Witwit A, Al-Ashtari A, Sandset PM.
404 Multidetector computed tomography (MDCT) in the diagnosis of pulmonary embolism:
405 interobserver agreement among radiologists with varied levels of experience. *Acta Radiol*.
406 2007;**48**:165-70. doi: 10.1080/02841850601100859.

- 407 9. Moores LK. Are We Overtreating Isolated Subsegmental Pulmonary Embolism?: First
408 Do No Harm. *JAMA internal medicine*. 2018;**178**:1274-5. doi:
409 10.1001/jamainternmed.2018.2970.
- 410 10. Gurney JW. No fooling around: direct visualization of pulmonary embolism.
411 *Radiology*. 1993;**188**:618-9. doi: 10.1148/radiology.188.3.8351321.
- 412 11. Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary
413 angiograms find pulmonary emboli that do not need to be found. *Bmj*. 2013;**347**:f3368. doi:
414 10.1136/bmj.f3368.
- 415 12. Bariteau A, Stewart LK, Emmett TW, Kline JA. Systematic Review and Meta-analysis
416 of Outcomes of Patients With Subsegmental Pulmonary Embolism With and Without
417 Anticoagulation Treatment. *Acad Emerg Med*. 2018;**25**:828-35. doi: 10.1111/acem.13399.
- 418 13. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST
419 Guideline and Expert Panel Report. *Chest*. 2016;**149**:315-52. doi:
420 10.1016/j.chest.2015.11.026.
- 421 14. Spencer FA, Gore JM, Lessard D, et al. Venous thromboembolism in the elderly. A
422 community-based perspective. *Thromb Haemost*. 2008;**100**:780-8.
- 423 15. Mean M, Righini M, Jaeger K, et al. The Swiss cohort of elderly patients with venous
424 thromboembolism (SWITCO65+): rationale and methodology. *J Thromb Thrombolysis*.
425 2013;**36**:475-83. doi: 10.1007/s11239-013-0875-2.
- 426 16. Jimenez D, Aujesky D, Diaz G, et al. Prognostic significance of deep vein thrombosis
427 in patients presenting with acute symptomatic pulmonary embolism. *Am J Respir Crit Care*
428 *Med*. 2010;**181**:983-91. doi: 10.1164/rccm.200908-1204OC.
- 429 17. Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the
430 emergency department: the revised Geneva score. *Annals of internal medicine*.
431 2006;**144**:165-71.
- 432 18. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic
433 model for pulmonary embolism. *Am J Respir Crit Care Med*. 2005;**172**:1041-6. doi:
434 10.1164/rccm.200506-862OC.

- 435 19. Klok FA, Cohn DM, Middeldorp S, et al. Quality of life after pulmonary embolism:
436 validation of the PEmb-QoL Questionnaire. *Journal of thrombosis and haemostasis : JTH.*
437 2010;**8**:523-32. doi: 10.1111/j.1538-7836.2009.03726.x.
- 438 20. Cohn DM, Nelis EA, Busweiler LA, Kaptein AA, Middeldorp S. Quality of life after
439 pulmonary embolism: the development of the PEmb-QoL questionnaire. *Journal of*
440 *thrombosis and haemostasis : JTH.* 2009;**7**:1044-6. doi: 10.1111/j.1538-7836.2009.03341.x.
- 441 21. Rochat M, Mean M, Limacher A, et al. Quality of life after pulmonary embolism:
442 validation of the French version of the PEmb-QoL questionnaire. *Health Qual Life Outcomes.*
443 2014;**12**:174. doi: 10.1186/s12955-014-0174-4.
- 444 22. Frey PM, Mean M, Limacher A, et al. Quality of life after pulmonary embolism:
445 Prospective validation of the German version of the PEmb-QoL questionnaire. *Thrombosis*
446 *research.* 2015;**135**:1087-92. doi: 10.1016/j.thromres.2015.03.031.
- 447 23. Akaberi A, Klok FA, Cohn DM, Hirsch A, Granton J, Kahn SR. Determining the
448 minimal clinically important difference for the PEmbQoL questionnaire, a measure of
449 pulmonary embolism-specific quality of life. *Journal of thrombosis and haemostasis : JTH.*
450 2018;**16**:2454-61. doi: 10.1111/jth.14302.
- 451 24. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the
452 optimal intensity of oral anticoagulant therapy. *Thromb Haemost.* 1993;**69**:236-9.
- 453 25. Aalen OO, Johansen S. An Empirical Transition Matrix for Non-Homogeneous Markov
454 Chains Based on Censored Observations. *Scandinavian Journal of Statistics.* 1978;**5**:141-
455 50.
- 456 26. Gray R. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a
457 Competing Risk. *The Annals of Statistics.* 1988;**16**:1141-54. doi: 10.1214/aos/1176350951
- 458 27. Fine J, & Gray, R. A Proportional Hazards Model for the Subdistribution of a
459 Competing Risk. *Journal of the American Statistical Association.* 1999;**94**:496-509. doi:
460 10.2307/2670170.
- 461 28. Heit JA, Lahr BD, Ashrani AA, Petterson TM, Bailey KR. Predictors of venous
462 thromboembolism recurrence, adjusted for treatments and interim exposures: a population-

- 463 based case-cohort study. *Thrombosis research*. 2015;**136**:298-307. doi:
464 10.1016/j.thromres.2015.06.030.
- 465 29. Franco Moreno AI, Garcia Navarro MJ, Ortiz Sanchez J, et al. A risk score for
466 prediction of recurrence in patients with unprovoked venous thromboembolism (DAMOVES).
467 *Eur J Intern Med*. 2016;**29**:59-64. doi: 10.1016/j.ejim.2015.12.010.
- 468 30. McRae S, Tran H, Schulman S, Ginsberg J, Kearon C. Effect of patient's sex on risk
469 of recurrent venous thromboembolism: a meta-analysis. *Lancet*. 2006;**368**:371-8. doi:
470 10.1016/s0140-6736(06)69110-1.
- 471 31. Huang W, Goldberg RJ, Anderson FA, Cohen AT, Spencer FA. Occurrence and
472 predictors of recurrence after a first episode of acute venous thromboembolism: population-
473 based Worcester Venous Thromboembolism Study. *J Thromb Thrombolysis*. 2016;**41**:525-
474 38. doi: 10.1007/s11239-015-1301-8.
- 475 32. Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep
476 vein thrombosis: incidence and risk factors. *Arch Intern Med*. 2000;**160**:769-74.
- 477 33. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism
478 severity index for prognostication in patients with acute symptomatic pulmonary embolism.
479 *Arch Intern Med*. 2010;**170**:1383-9. doi: 10.1001/archinternmed.2010.199.
- 480 34. Spirk D, Husmann M, Hayoz D, et al. Predictors of in-hospital mortality in elderly
481 patients with acute venous thrombo-embolism: the SWISS Venous ThromboEmbolic
482 Registry (SWIVTER). *European heart journal*. 2012;**33**:921-6. doi: 10.1093/eurheartj/ehr392.
- 483 35. Seiler E, Limacher A, Mean M, et al. Derivation and validation of a novel bleeding risk
484 score for elderly patients with venous thromboembolism on extended anticoagulation.
485 *Thromb Haemost*. 2017;**117**:1930-6. doi: 10.1160/th17-03-0162.
- 486 36. Le Gal G, Righini M, Parent F, van Strijen M, Couturaud F. Diagnosis and
487 management of subsegmental pulmonary embolism. *Journal of thrombosis and haemostasis*
488 : *JTH*. 2006;**4**:724-31. doi: 10.1111/j.1538-7836.2006.01819.x.
- 489 37. Auer RC, Schulman AR, Tuorto S, et al. Use of helical CT is associated with an
490 increased incidence of postoperative pulmonary emboli in cancer patients with no change in

- 491 the number of fatal pulmonary emboli. *J Am Coll Surg*. 2009;**208**:871-80. doi:
492 10.1016/j.jamcollsurg.2008.12.030.
- 493 38. Pesavento R, Casazza F, Filippi L, Milan M, Monreal M, Prandoni P. An international
494 survey on isolated subsegmental pulmonary embolism. *Thrombosis research*. 2013;**131**:183-
495 4. doi: 10.1016/j.thromres.2012.11.017.
- 496 39. Kline JA, Hogg MM, Courtney DM, Miller CD, Jones AE, Smithline HA. D-dimer
497 threshold increase with pretest probability unlikely for pulmonary embolism to decrease
498 unnecessary computerized tomographic pulmonary angiography. *Journal of thrombosis and*
499 *haemostasis : JTH*. 2012;**10**:572-81. doi: 10.1111/j.1538-7836.2012.04647.x.
- 500 40. Angriman F, Ferreyro BL, Posadas-Martinez ML, Giunta D, Vazquez FJ, Vollmer WM.
501 Wells Score and Poor Outcomes Among Adult Patients With Subsegmental Pulmonary
502 Embolism: A Cohort Study. *Clin Appl Thromb Hemost*. 2015;**21**:539-45. doi:
503 10.1177/1076029614559772.
- 504 41. Nijkeuter M, Kwakkel-van Erp JM, Kruij MJ, et al. Incidence of diagnosis of
505 subsegmental pulmonary emboli using multidetector row and single-detector row computed
506 tomography. *Journal of thrombosis and haemostasis : JTH*. 2008;**6**:384-6. doi:
507 10.1111/j.1538-7836.2007.02832.x.
- 508 42. Metter D, Tulchinsky M, Freeman LM. Current Status of Ventilation-Perfusion
509 Scintigraphy for Suspected Pulmonary Embolism. *AJR Am J Roentgenol*. 2017;**208**:489-94.
510 doi: 10.2214/ajr.16.17195.
- 511 43. Gomez-Outes A, Terleira-Fernandez AI, Lecumberri R, Suarez-Gea ML, Vargas-
512 Castrillon E. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a
513 systematic review and meta-analysis. *Thrombosis research*. 2014;**134**:774-82. doi:
514 10.1016/j.thromres.2014.06.020.
- 515 44. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of
516 antihemostatic medicinal products in non-surgical patients. *Journal of thrombosis and*
517 *haemostasis : JTH*. 2005;**3**:692-4. doi: 10.1111/j.1538-7836.2005.01204.x.

519 **FIGURE LEGENDS**

520 **Figure 1.**

521 Patient flow chart.

522

523 **Figure 2.**

524 **a. Aalen-Johansen estimates of recurrent VTE by localization of PE**

525 The 3-year cumulative incidence of recurrent VTE was 7% in patients with isolated
526 SSPE and 12% in patients with more proximal PE (P=0.413 by the Gray-test).

527

528 **b. Kaplan-Meier estimates of overall mortality by localization of PE**

529 The 3-year cumulative incidence of overall mortality was 29% in patients with isolated
530 SSPE and 20% in patients with more proximal PE (P=0.086 by the log-rank test).

Table 1. Patient baseline characteristics and treatments by localization of PE

	All (N=578)	Isolated SSPE (N=64)	Proximal PE (N=514)	
Characteristics ^a	n (%) or median (interquartile range)			P-value
Baseline characteristics				
Patient age, years	75 (70; 81)	76 (69; 81)	74 (70; 81)	0.85
Male sex	308 (53)	27 (42)	281 (55)	0.06
VTE risk factors				
Active cancer ^b	94 (16)	18 (28)	76 (15)	0.01
Immobilisation ^c	127 (22)	11 (17)	116 (23)	0.33
Major surgery ^d	91 (16)	11 (17)	80 (16)	0.74
Current oestrogen therapy ^e	19 (3)	4 (6)	15 (3)	0.16
History of VTE	155 (27)	15 (23)	140 (27)	0.52
Comorbid conditions				
Chronic heart failure	42 (7)	5 (8)	37 (7)	0.86
Chronic lung disease	93 (16)	14 (22)	79 (15)	0.18
History of major bleeding ^f	64 (11)	6 (9)	58 (11)	0.68
Clinical symptoms & signs of VTE				
Acute chest pain ^g	280 (48)	35 (55)	245 (48)	0.29
New or worsening dyspnoea ^g	472 (82)	47 (73)	425 (83)	0.07
New unilateral leg pain or swelling ^g	129 (22)	17 (27)	112 (22)	0.39
Confirmed distal DVT ^h	28 (5)	2 (3)	26 (5)	0.50
Pulse \geq 110/min.	71 (12)	2 (3)	69 (13)	0.02
Systolic BP <100 mm Hg	22 (4)	2 (3)	20 (4)	0.81
Respiratory rate \geq 30/min.	20 (3)	0 (0)	20 (4)	0.12
Body temperature <36°C	43 (7)	4 (6)	39 (8)	0.75
Altered mental status ⁱ	20 (3)	0 (0)	20 (4)	0.11
Arterial O ₂ saturation <90%	89 (15)	6 (9)	83 (16)	0.20

(continued)

Characteristics	All	Isolated	Proximal PE	P-value
	(N=578)	SSPE (N=64)	(N=514)	
	n (%) or median (interquartile range)			
Clinical probability for PE [17]				0.54
Low	98 (17)	9 (14)	89 (17)	-
Intermediate	427 (74)	47 (73)	380 (74)	-
High	53 (9)	8 (13)	45 (9)	-
PESI risk classes [18]				0.51
I	4 (1)	1 (2)	3 (1)	-
II	192 (33)	22 (34)	170 (33)	-
III	177 (31)	18 (28)	159 (31)	-
IV	131 (23)	18 (28)	113 (22)	-
V	74 (13)	5 (8)	69 (13)	-
Diagnostic method				<0.001
Positive spiral CT	520 (90)	47 (73)	473 (92)	-
Pulmonary angiography	2 (0)	1 (2)	1 (0)	-
High-probability ventilation/perfusion lung scintigraphy	56 (10)	16 (25)	40 (8)	-
Laboratory findings				
Hs-cTNT, pg/mL	15 (8; 32)	15 (6; 28)	15 (8; 33)	0.57
NT-proBNP, pg/mL	571 (209; 1566)	547 (272; 1386)	577 (205; 1644)	0.95
D-dimer, ng/mL	2341 (1505; 3560)	2005 (1087; 3651)	2361 (1531; 3545)	0.09
Anemia ⁱ	221 (38)	28 (44)	193 (38)	0.23
Thrombocytopenia ^k	83 (14)	6 (9)	77 (15)	0.26
VTE-related treatment				
Type of AC started within 1 month of PE				
VKA therapy ^l	518 (90)	51 (80)	467 (91)	0.01
Parenteral AC ^m	564 (98)	61 (95)	503 (98)	0.21

(continued)

Characteristics	All	Isolated	Proximal PE	P-value
	(N=578)	SSPE (N=64)	(N=514)	
	n (%) or median (interquartile range)			
No initial AC	4 (1)	1 (2)	3 (1)	0.37
Thrombolysis ⁿ	19 (3)	0 (0)	19 (4)	0.12
Inferior vena cava filter	8 (1)	0 (0)	8 (2)	0.32
Concomitant treatments				
Antiplatelet drugs/NSAIDs ^o	237 (41)	29 (45)	208 (40)	0.46
Outpatient management^p	28 (5)	7 (11)	21 (4)	0.02

Abbreviations: (SS)PE= (subsegmental) pulmonary embolism; VTE= venous thromboembolism; DVT= deep vein thrombosis; BP= blood pressure; CT= computed tomography; Hs-cTNT= high-sensitivity cardiac troponin T; VKA= vitamin K antagonists; AC= anticoagulation; NSAID= non-steroidal anti-inflammatory drugs.

^aData were missing for pulse (1%), systolic BP (1%), respiratory rate (22%), body temperature (2%), arterial O₂ saturation (6%), Hs-cTNT (13%), NT-proBNP (13%), D-dimer (15%), anemia (2%), and thrombocytopenia (2%).

^bSolid or hematologic cancer requiring chemotherapy, radiotherapy, surgery, or palliative care during the last 3 months.

^cBed rest >72 hours, voyage in sitting position for >6 hours, fracture or cast of the lower extremity during the last 3 months.

^dSurgery requiring general or spinal anaesthesia during the last 3 months.

^eAny oestrogen-containing treatment such as osteoporosis prevention/treatment, oral hormone replacement therapy, or antitumor treatment for breast or prostate cancer during the last 3 months.

^fHistory of a symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in haemoglobin level of ≥ 20 g/L, or leading to transfusion of ≥ 2 units of whole blood or red cells [44].

^gDuring the last 21 days.

^hConfirmed by compression ultrasonography or contrast venography.

ⁱDisorientation, lethargy, stupor, or coma.

^jHaemoglobin <13 g/dL in men or <12 g/dL in women.

^kPlatelet count <150 G/L.

^lAcenocoumarol or phenprocoumon.

^mIntravenous or subcutaneous unfractionated heparin, dalteparin, enoxaparin, nadroparin, fondaparinux, or other.

ⁿSystemic or catheter-directed thrombolysis.

^oAspirin, clopidogrel, prasugrel, aspirin/dipyridamol, or any NSAID (e.g., ibuprofen).

^pHospital stay for <24 hours.

Table 2. Clinical outcomes by localization of PE

Clinical outcomes	All (N=578)	Isolated SSPE (N=64)	Proximal PE (N=514)	P-value
	n (%)			
Recurrent VTE				
At 3 months	7 (1)	1 (2)	6 (1)	0.56
Entire follow-up period	59 (10)	5 (8)	54 (11)	0.66
Recurrent PE				
At 3 months	6 (1)	1 (2)	5 (1)	0.51
Entire follow-up period	45 (8)	3 (5)	42 (8)	0.46
Recurrent DVT				
At 3 months	1 (0)	0 (0)	1 (0)	1.00
Entire follow-up period	17 (3)	2 (3)	15 (3)	1.00
Overall mortality				
At 3 months	31 (5)	7 (11)	24 (5)	0.07
Entire follow-up period	115 (20)	18 (28)	97 (19)	0.10
Definite or possible PE-related death				
During the index hospitalization	7 (1)	0 (0)	7 (1)	1.00
At 3 months	11 (2)	1 (2) ^a	10 (2) ^b	1.00
Entire follow-up period	23 (4)	2 (3) ^c	21 (4) ^d	0.52

Abbreviations: (SS)PE= (subsegmental) pulmonary embolism; VTE= venous thromboembolism; DVT= deep vein thrombosis.

^aCause of death was adjudicated as possibly related to PE.

^bCause of death was adjudicated as definitely due to PE in 3 patients and as possibly related to PE in 7 patients.

^cCause of death was adjudicated as possibly related to PE in both patients.

^dCause of death was adjudicated as definitely due to PE in 6 patients and as possibly related to PE in 15 patients.

Table 3. Association between localization of PE and VTE recurrence or overall mortality

	All PE diagnosis (N=578)	CTPA-based PE diagnosis only (N=520)
Adjusted sub-hazard ratio (95%CI)		
VTE recurrence		
Proximal PE	Reference	Reference
Isolated SSPE	0.64 (0.25–1.62) ^a	0.57 (0.20–1.62) ^a
Adjusted hazard ratio (95%CI)		
Overall mortality		
Proximal PE	Reference	Reference
Isolated SSPE	1.12 (0.64–1.96) ^c	1.34 (0.71–2.53) ^c

Abbreviations: (SS)PE= (subsegmental) pulmonary embolism; CTPA= computed tomography pulmonary angiography; CI= confidence interval; VTE= venous thromboembolism.

^aAdjusted for age, sex, active cancer, prior VTE, and periods of anticoagulation as a time-varying covariate.

^bAdjusted for age, sex, previous major bleeding, active cancer, low physical activity, anemia, thrombocytopenia, antiplatelet or non-steroidal anti-inflammatory drugs, and periods of anticoagulation as a time-varying covariate.

Table 4. Duration of anticoagulation by localization of PE

	All (N=527) ^a	Isolated SSPE (N=56)	Proximal PE (N=471)	
	n (%) or median (interquartile range)			P-value
Duration of initial AC, months	12.2 (6.2; 28.0)	10.7 (6.1; 24.1)	12.3 (6.3; 28.7)	0.34
Duration of initial AC				0.35
≤3 months	38 (7)	7 (13)	31 (7)	-
3–6 months	74 (14)	6 (11)	68 (14)	-
6–12 months	147 (28)	17 (30)	130 (28)	-
>12 months	268 (51)	26 (46)	242 (51)	-

Abbreviations: (SS)PE= (subsegmental) pulmonary embolism; AC= anticoagulation.

^aPatients who died within the first 6 months were excluded from this analysis (N=51).

Table 5. Quality of oral anticoagulant by localization of PE

INR range ^a	All	Isolated SSPE	Proximal PE	P-value
	(N=494)	(N=48)	(N=446)	
	median % of time (interquartile range)			
2.0–3.0	65.1 (48.1; 80.5)	66.4 (45.3; 82.2)	65.0 (48.1; 80.5)	0.71
>3.0	10.4 (3.1; 20.5)	11.4 (3.2; 20.3)	10.3 (3.1; 20.6)	0.91
<2.0	15.7 (6.3; 33.3)	15.5 (3.9; 30.6)	15.7 (6.6; 33.5)	0.55

Abbreviations: (SS)PE= (subsegmental) pulmonary embolism; INR= international normalized ratio.

^aOnly patients with initial vitamin K antagonist treatment and at least two INR measurements were considered.

Figure 1.

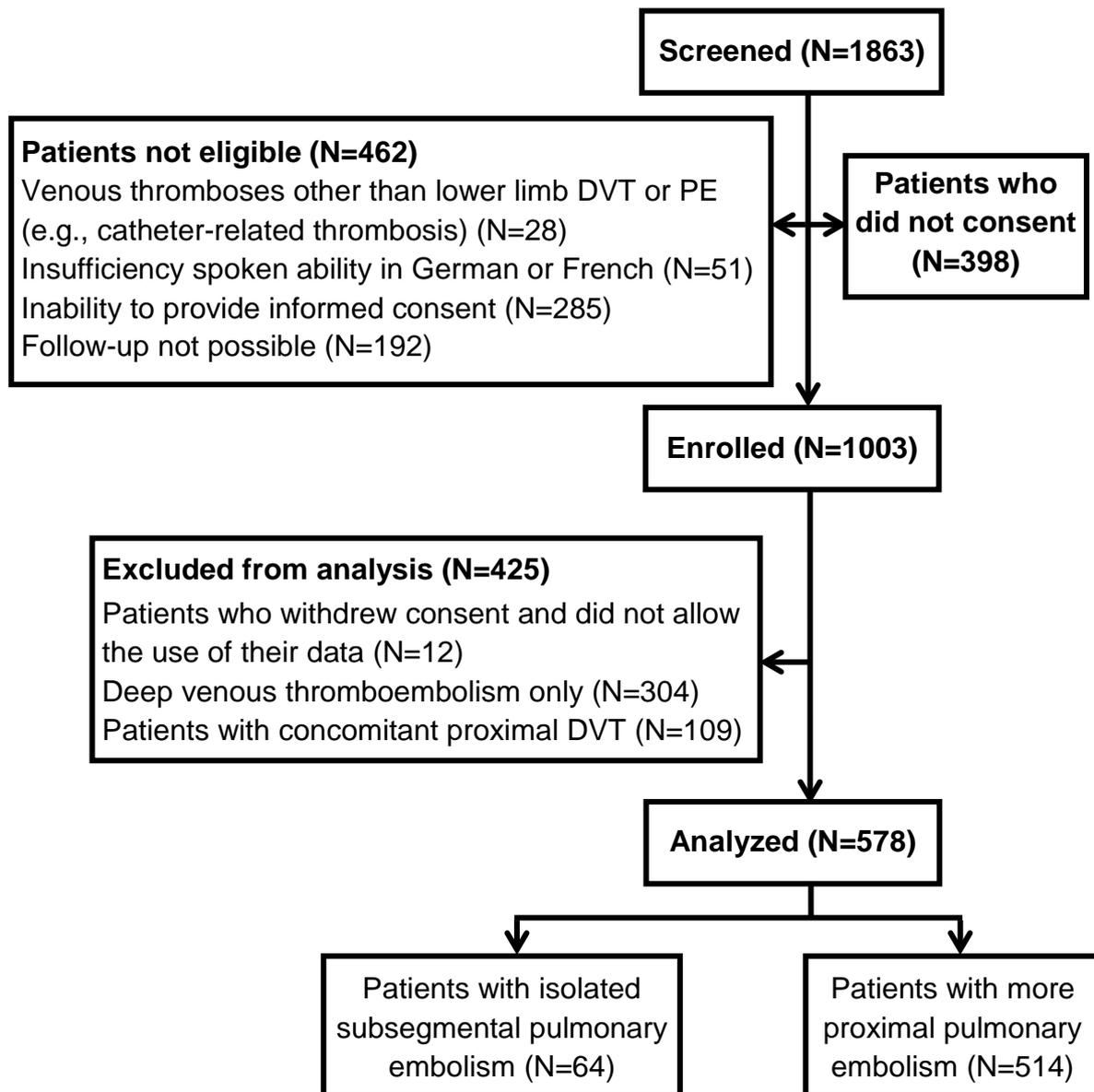
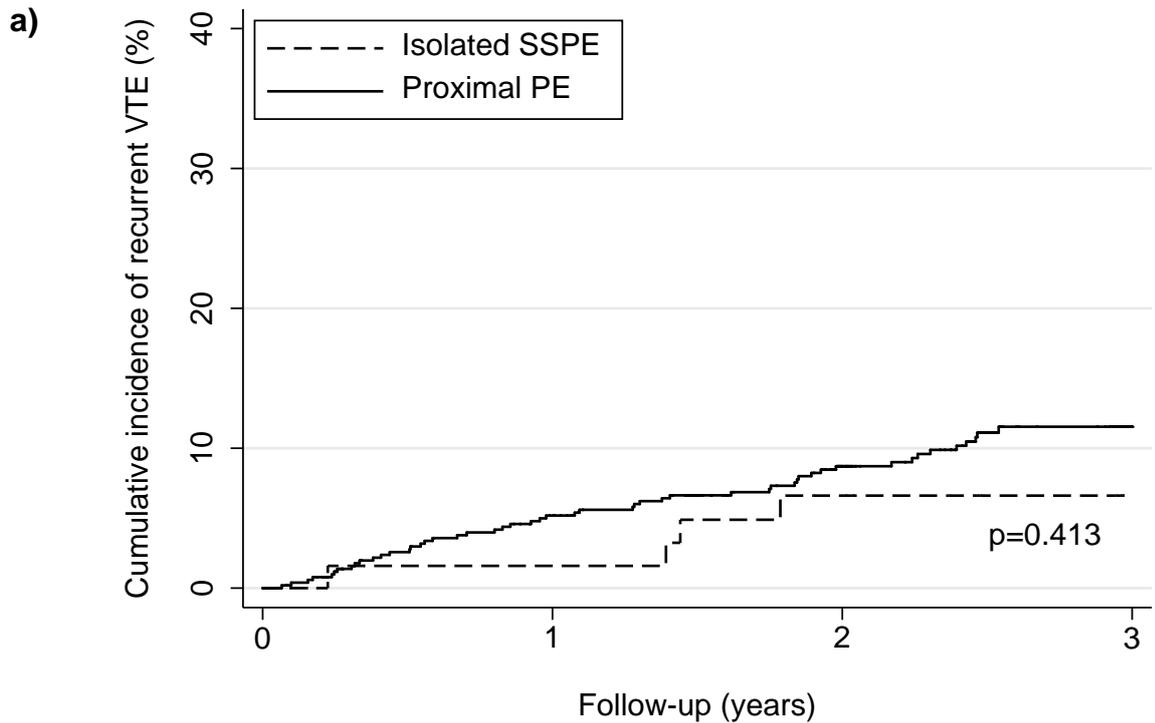
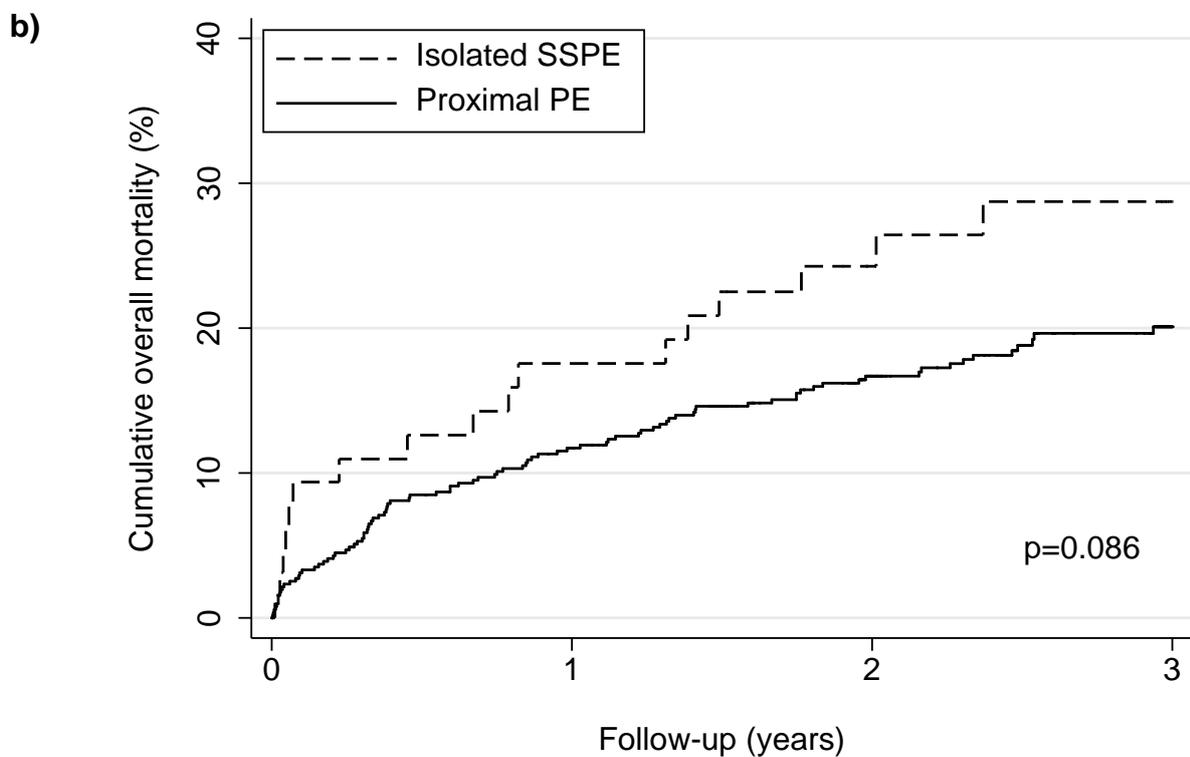


Figure 2.



Number at risk					
Isolated SSPE	64		60		35
Proximal PE	514		467		337
					16
					114



Number at risk					
Isolated SSPE	64		50		37
Proximal PE	514		435		314
					17
					131