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Early prescription of direct oral anticoagulant for the treatment of intermediate-high risk pulmonary embolism: a multi-center, observational cohort study

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1 **Original article**

2 ***Thrombosis Research***

3 **Early prescription of direct oral anticoagulant for the treatment of intermediate-high risk**
4 **pulmonary embolism: a multi-center, observational cohort study**

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16

17 **Word count:** 3,008

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28

29 **Highlights:**

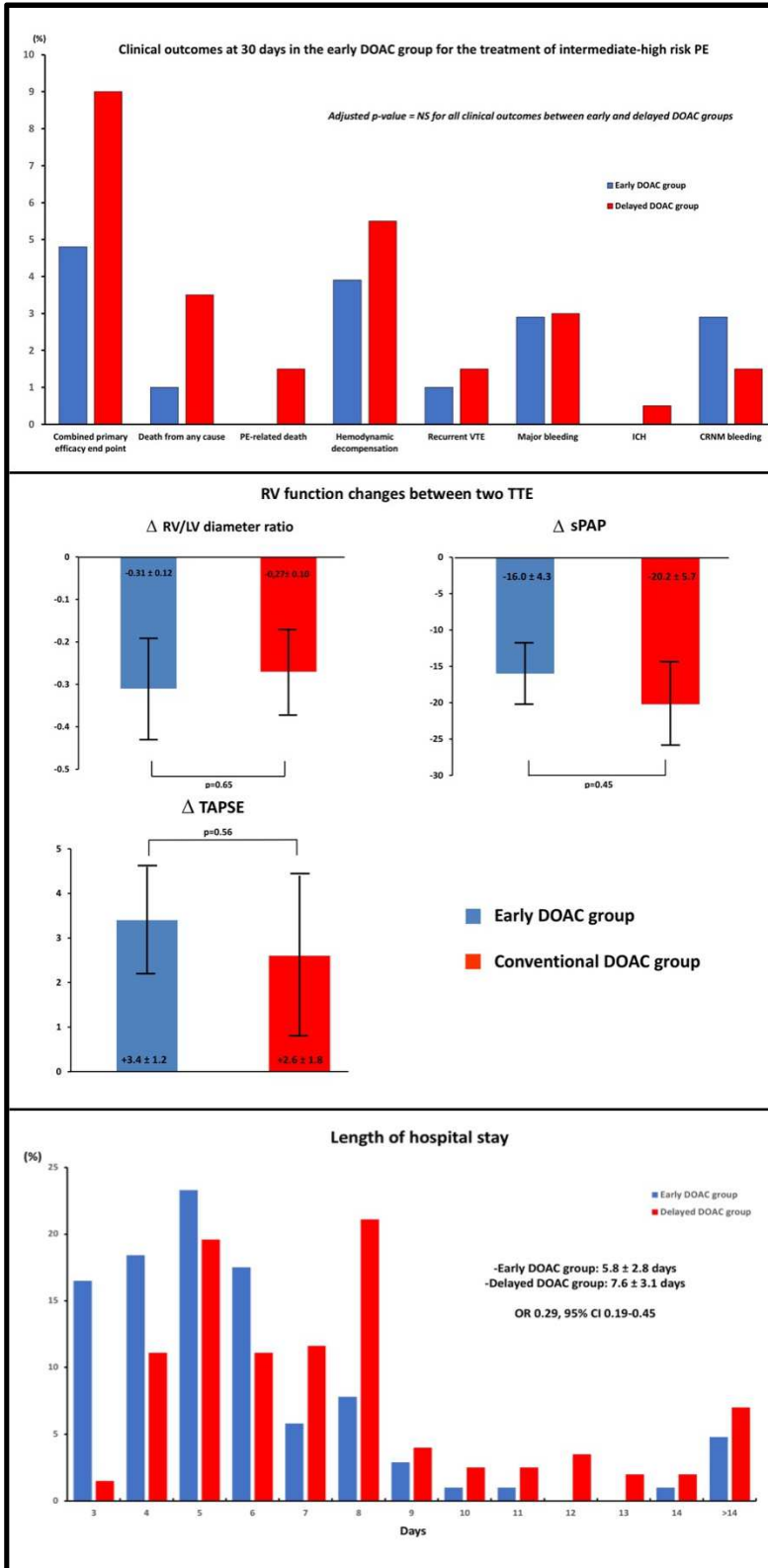
30 -One third of intermediate-high risk PE patients treated with DOAC receive them early

31 -The rate of outcomes in patient receiving a DOAC early after admission was low

32 -Early DOAC pts were discharged earlier

33 -Adverse outcome rates were similar between groups.

34 Graphical Abstract



35

36 **Abstract**

37 **Objectives:** The safety and efficacy of direct oral anticoagulants (DOACs) in intermediate-high
38 risk pulmonary embolism (PE) are unknown. The aims of the present study were to describe
39 outcomes of patients receiving early apixaban or rivaroxaban prescription rather the
40 recommended delayed prescription strategy.

41 **Methods:** Retrospective *post-hoc* analysis based on prospectively collected data form a
42 multicenter cohort including all consecutive PE patients stratified as intermediate-high risk.
43 Group definitions were: early group with DOAC prescription <72 hours after admission; delayed
44 group with DOAC prescription between 72 hours and discharge. The 30-day primary efficacy
45 outcome was a clinical composite of all-cause death and hemodynamic decompensation. The
46 30-day primary safety outcome was major bleeding.

47 **Results:** Among 2,411 patients admitted with PE, 302 were treated with a DOAC for an
48 intermediate-high risk PE. 34.2% in the early group and 65.9% in the delayed group. The
49 primary outcome occurred 4.8% (including 1 death and 4 hemodynamic decompensations) in
50 the early DOAC group and in 9.0% in the delayed DOAC group (OR, 0.44, 95% CI 0.15-1.30). The
51 rate of major bleeding did not differ between groups (OR, 0.99; 95% CI 0.45-2.18). The length of
52 stay was numerically shorter in the early group whereas the other outcomes did not differ
53 significantly.

54 **Conclusion:** The rate of 30-day outcomes was low in patient receiving a DOAC earlier after
55 admission. Patients in the early DOAC group had a numerically shorter length of stay, with
56 similarly low rates of death and bleeding, and similar RV function recovery compared to the
57 delayed strategy.

58 **Abstract word counts:** 249

59

60 **Key words:** pulmonary embolism, direct oral anticoagulant, outcomes

61 **Introduction**

62 The European Society of Cardiology (ESC) guidelines stratify a sub-group of hemodynamically
63 stable pulmonary embolism (PE) patients with right ventricular (RV) dysfunction and elevation
64 of troponin stratified as intermediate-high risk [1]. This PE category has 30-day mortality of
65 3.0% and most adverse events occur within the first 72 hours [2]. Direct oral anticoagulants
66 (DOACs) have demonstrated a better safety profile than the standard low molecular weight
67 heparin (LMWH)/warfarin regimen [3]. The factor X-inhibitors rivaroxaban and apixaban were
68 tested with a single-drug approach, do not require parenteral anticoagulation, and were
69 associated with shorter hospital stay [4-6].

70 The utility of initial high dose rivaroxaban and apixaban to prevent early venous
71 thromboembolism (VTE) recurrence in intermediate-high risk PE was not evaluated in
72 randomized trials [4, 5]. Accordingly, and given the potential need for thrombolysis if
73 hemodynamic failure occurs, practice guidelines recommend initial parenteral anticoagulation
74 for at least 3 days in intermediate-high risk PE [1].

75 The aim of this pilot study was to describe 30-day outcomes of intermediate-high risk
76 patients receiving rivaroxaban or apixaban within the first 72 hours. We also compared these
77 patients to those treated with the guidelines-defined delayed DOAC approach.

78

79 **Material and methods**

80 This cohort study is a non-interventional retrospective *post-hoc* analysis based on prospectively
81 collected data from 7 French centers, including two tertiary care facilities and five general
82 hospitals, and recorded in the BFC-FRANCE registry [7]. We report the study methods and

83 results in accordance with the STrengthening the Reporting of Observational studies in
84 Epidemiology (STROBE) guidelines [8]. In accordance with current French legislation, informed
85 consent was not required for the analysis of patient data, because the study did not modify
86 diagnostic or therapeutic strategies. The study received approval from the National the national
87 commission for data privacy and protection (CNIL) (under the number 917 149).

88 ***Patients, setting, and participants***

89 We screened patients who were admitted between September 2012 and November 2019 at 7
90 cooperating centers. Inclusion criteria were: (1) consecutive patients aged 18 years or older
91 with a diagnosis of PE confirmed by computed tomography pulmonary angiography or
92 ventilation-perfusion scan. For confirmation of the diagnosis of PE, we required an intraluminal
93 filling defect on CTPA [9]; or a high probability V-Q scan according to the criteria of the
94 Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) [10]; (2) PE stratified as
95 intermediate-high risk according to the 2019 ESC guidelines including hemodynamic stability
96 (systolic blood pressure > 90 mmHg and no sign of end-organ hypoperfusion), simplified
97 Pulmonary Embolism Severity Index (sPESI) score ≥ 1 , elevation of troponin and RV dysfunction
98 on transthoracic echocardiography (TTE) performed at admission [1]; and (3) patients had to
99 have received treatment with apixaban or rivaroxaban during the in-hospital course. sPESI
100 score was assessed as previously described (1 point for each of the following: age >80 years,
101 systolic blood <100 mmHg, heart rate ≥ 110 beats per minute (bpm), oxygen saturation <90%,
102 history of cancer, congestive heart failure or pulmonary diseases) [11]. Different assays for
103 troponin I measurement were used over time (ACS:180 before 2014, and Elecsys thereafter,
104 ROCHE, Basel, Switzerland). Cardiac troponin elevation was defined as a value above the 99th

105 percentile of healthy subjects with a coefficient of variation of 10% for the test used. Trans-
106 thoracic echography was performed in routine practice at least at admission and at 48 hours.
107 Right ventricle dysfunction was defined by the presence of at least one of the following on
108 echography: increased end-diastolic RV/left ventricle (LV) diameter ≥ 1.0 in the apical four-
109 chamber view, Flattened intraventricular septum, decrease tricuspid annular plane systolic
110 (TAPSE) excursion < 16 mm, or right heart thrombus detected in right heart cavities [1].

111 **Data collection**

112 All sites followed a standardized protocol, as previously described [7]. Baseline characteristics,
113 in-hospital therapies and adverse events were prospectively recorded by research physicians.
114 One month after diagnosis, patients returned to the hospital for a follow-up visit. If the patient
115 failed to attend (12.0%), the following sequential procedure was followed: telephone interview
116 with the patient (or family), consultation of hospitalization records since discharge, telephone
117 contact with the patient's physicians, consultation of the national death registry.

118 Vascular disease included coronary artery disease, stroke, or peripheral arterial disease.
119 Active cancer was defined by a cancer being treated, symptomatic, or palliated within the last 6
120 months. Bleeding risk was estimated with the modified HAS-BLED score [12].

121 **Early versus delayed DOAC prescription**

122 Early DOAC prescription with apixaban (Bristol-Myers Squibb/Pfizer, New-York, USA) or
123 rivaroxaban (Bayer HealthCare AG, Leverkusen, Germany) was defined as prescription < 72
124 hours after admission, either without heparin or after a short lead-in period with heparin (early
125 DOAC group). Delayed DOAC was defined as prescription at 72 hours or beyond (delayed DOAC

126 group). Participation to the study was not supposed to change the therapeutic approach in any
127 way, and management of acute PE was at the discretion of the physicians in charge.

128 The study period encompassed September 2012 through November 2019. We chose
129 September 2012 as the starting point of this study as it corresponded to the launch date of the
130 direct inhibitor of activated factor X rivaroxaban, the first DOAC to be approved on our national
131 market for the dedicated indication of acute PE treatment. The direct inhibitor of activated
132 factor X, apixaban, was authorized in this indication from April 2015 onwards (edoxaban
133 (Daiichi Sankyo, Tokyo, Japan) and the direct inhibitor of activated factor II, dabigatran
134 (Boehringer Ingelheim, Ingelheim am Rhein, Germany) were not approved for the treatment of
135 acute PE in the market during the study period).

136 **Outcomes and definitions**

137 The primary efficacy outcome was a composite of all-cause death or hemodynamic
138 decompensation at 30 days. Secondary efficacy outcomes at 30 days included a composite of
139 PE-related death or hemodynamic decompensation, as well as recurrent VTE, length of hospital
140 stay, and in-hospital recovery of RV function. The primary safety outcome was 30-day major
141 bleeding. The secondary safety outcome at 30 days was clinically relevant non-major (CRNM)
142 bleeding and Intra-cranial hemorrhage.

143 Hemodynamic decompensation was defined as presence of cardiogenic shock or sustained
144 hypotension justifying advanced therapies including systemic thrombolysis, surgical
145 embolectomy or extra-corporeal membrane oxygenation (ECMO). RV function recovery
146 included absolute change in RV/left ventricle (LV) diastolic diameter ratio, systolic pulmonary
147 artery pressure, (sPAP), and tricuspid annulus plane systolic excursion (TAPSE) assessed by

148 trans-thoracic echocardiography (TTE) performed at admission and at 48 hours. Bleeding events
149 were classified according to the International Society of Thrombosis and Haemostasis criteria
150 [13]. All suspected outcome events were classified by a central adjudication committee (CE and
151 FS) whose members were unaware of the DOAC strategy (i.e. early vs delayed). An independent
152 data safety monitoring board periodically reviewed outcome. Disagreement was solved by a
153 third author (RC).

154 **Statistical analysis**

155 Statistical analyses were performed according the SAMPL guidelines. Continuous variables are
156 expressed as mean \pm standard deviation (SD) when normally distributed, or median \pm
157 interquartile range if not normally distributed, and were analysed with the Student t test or
158 Wilcoxon rank sum test as appropriate. Categorical variables are described as number
159 (percentage) and were compared with the chi-square test or Fisher's exact test. The
160 multivariable models included a missing indicator if a variable had more than 10% of missing
161 values and the variable sites of care. To investigate the independent associations of various
162 characteristics with the prescription or non-prescription of DOACs in the acute phase of
163 intermediate-high risk PE, as well as the association with early and delayed DOAC prescription,
164 we constructed a hierarchical modified Poisson regression models with robust error variance,
165 adjusted for patient and practice-level characteristics. Covariates entered into the model were
166 all baseline characteristics including socio-demographic, clinical and biological data and imaging
167 findings. Because the rate of DOAC prescription exceeded 10%, we used modified Poisson
168 regression at all steps to estimate relative prescription rates (relative risk, RR) with 95%
169 confidence intervals (CI) directly (instead of odds ratios (OR) obtained from logistic regression,

170 which may overestimate effect differences) [14]. We compared 30-day primary clinical
171 outcomes from patients treated with early versus those treated with guidelines-defined
172 delayed DOAC prescription by using a logistic regression. Results are reported as OR with
173 associated 95% CI. A p-value <0.05 was considered significant for the primary endpoint; all
174 other analyses are exploratory [15]. All analyses were performed using SAS version 9.4 (SAS
175 Institute Inc., Cary, NC, USA).

176 **Results**

177 ***Study sample***

178 Among 2,411 patients admitted to participating centers with a confirmed diagnosis of PE during
179 the study period, 653 (27.0%) were stratified as intermediate-high risk for early mortality
180 according to the ESC guidelines. Among them, 351 (53.7%) did not receive a DOAC during the
181 hospital stay, (249 patients (70.9%) received LMWH of whom 122 switched to vitamin K
182 antagonist (VKA); and 102 patients (29.1%) received intra-venous unfractionated heparin
183 followed by VKA) (mean age, 76.2 ± 13.9 ; 57.1% were women) (Table S1 in the supplementary
184 material). Poisson regression adjustment identified active cancer (OR, 0.02; 95% CI, 0.007-0.08),
185 renal function impairment (OR, 0.42, 95% CI 0.20-0.89) and prior vascular disease treated with
186 an antiplatelet therapy (OR, 0.73, 95% CI 0.45-0.88) as being associated with the non-
187 prescription of a DOAC during the hospital course. The rate of the primary end-point was higher
188 in patients not treated with a DOAC as compared to those who received a DOAC during the
189 hospital course, mainly driven by cancer-related death (Table S2, in the supplementary
190 material).

191 The remaining 302 patients (46.2%) were treated with a DOAC between admission and
192 discharge and composed the study population (mean age, 76.5 ± 13.6 years in average; 62.2%
193 were women) (Figure 1). All the 302 patients included in the study population underwent a TTE
194 at admission and at 48 hours.

195 Overall, 103 patients (34.2%; 95% CI, 28.8-39.8) were in the early group and 199 patients
196 (65.8%; 95% CI, 60.1-71.1) were in the delayed group (Table 1). Patients who received early
197 DOAC prescription were treated with rivaroxaban in 83.8% and apixaban in 16.2%, vs 85.1% and
198 14.9% respectively in the delayed DOAC group. Median time to DOAC introduction was 36
199 hours [24-48] in the early group including 15 patients who received a DOAC first without
200 heparin lead-in. Median time to DOAC introduction in the delayed group was 96 hours [72-120]
201 (all had heparin lead-in).

202 Patients in the early group were aged 75.8 ± 16.0 years in average; 63.1% were women
203 (Table 1). The most frequent co-morbidities were coronary disease (20.4%) and prior VTE
204 (26.2%). The primary outcome occurred in 5 out of 103 patients (4.8%; 95% CI, 1.6-10.9),
205 including 1 death and 4 hemodynamic decompensations. The cause of death of the patient who
206 died during the follow-up was infection. All 4 patients who developed hemodynamic
207 decompensation in the early group received low dose systemic thrombolysis (50 mg of rt-PA),
208 and did not experience any adverse events at 30 days. None of the 15 patients who received a
209 DOAC without heparin lead-in experienced an adverse event during follow-up. The rate of
210 secondary outcomes in the early group were: 1.0% (95% CI, 0.03-5.34) for recurrent VTE and
211 2.9% (95% CI, 0.6-8.3) for the composite of PE-related death or hemodynamic decompensation
212 (Table 2). The length of hospital stay in this group was 6.0 ± 3.6 days (Figure 2). Normalization

213 of RV function was observed by TTE for 95/103 patients (92.2%). Changes in RV function
214 parameters in the early group are displayed in Figure 3. The rate of major bleeding was 2.9%
215 (95% CI, 0.6-8.3) including no intra-cranial hemorrhage, and 3 patients experienced CRNM
216 (Table 2).

217 Overall, patients in the early group and those in the delayed group did not differ significantly
218 in terms of demographic data, pre-existing medical conditions, and in terms of relevant hospital
219 parameters. The HAS-BLED and the sPESI scores, as well as the Charlson comorbidities index
220 were similar between groups (Table 1). Site of care, outpatient vs inpatient, and conventional
221 ward vs intensive care unit were similar between groups.

222 In total, 23/302 patients (7.6%; 95% CI, 4.8-11.2%) died or suffer from a hemodynamic
223 decompensation during the first month of follow-up (i.e., primary efficacy outcome). The rate
224 of 30-day all-cause mortality was 2.6% (95% CI, 1.1-5.1) (8/302 patients)). Pulmonary embolism
225 (definite (n=5) or possible (n=1)) was the primary cause of death (75.0%) followed by infection
226 (12.5%), and bleeding (12.5%). All the 15 hemodynamic decompensations (4.9%, 95% CI 2.8-
227 8.0%) were treated with systemic thrombolysis without used of surgical embolectomy or
228 ECMO. Recurrent VTE was observed for 1.3% of patients (95% CI, 0.3-3.3%) (4/302 patients)
229 (Table 2). The mean length of hospital stay was 7.2 ± 1.3 days (Figure 2). The average changes in
230 RV/LV diameter ratio, in sPAP, and in TAPSE between two TTE performed at admission and at
231 48 hours were -0.29 ± 0.12 mm, -18.3 ± 4.4 mmHg, and $+2.9 \pm 1.1$ mm, respectively (Figure 3).
232 The rates of safety outcomes were 3.0% (95% CI, 1.4-5.6%) (9/302 patients) for major bleeding
233 at 30 days (i.e., primary safety outcome), and 2.0% (95% CI, 0.7-4.3) (6/302 patients) for CRNM

234 bleeding at 30 days. One intra-cranial hemorrhage (0.3%; 95% CI, 0.01-1.8) occurred within the
235 first month of follow-up (Table 2).

236 In univariate analysis, male sex, age (per quartile), saddle PE, and systolic blood pressure at
237 admission were significantly associated with the primary composite outcome all-cause death or
238 hemodynamic decompensation (Table 3). The relative risk for early DOAC prescription
239 regarding the occurrence of the primary outcome in univariate analysis was 0.38 (95% CI, 0.11-
240 1.38) (Table 3). The rate of the primary efficacy outcome was numerically higher in the delayed
241 group as compared to the early group but without reaching statistical significance after
242 multivariable adjustment (4.8% vs 9.0%; absolute difference, 4.2%; OR, 0.44 (95% CI 0.15-
243 1.30)). Secondary clinical efficacy outcomes, including the composite of PE-related death and
244 hemodynamic decompensation, as well as recurrent VTE, were numerically similar between
245 both groups (Table 2). The adjusted length of stay was numerically lower in the early group
246 (Figure 2). In total, 180/199 patients had RV function recovery in the delayed group (90.4%, $p =$
247 0.65 vs early DOAC group). Overall, no patient had clinical signs of pre-existing chronic
248 thromboembolic pulmonary hypertension on TTE at admission. We did not observe any
249 difference in RV function recovery between groups (Figure 3). There was no significant
250 difference in primary safety outcome (OR, 0.99; 95% CI 0.45-2.18) or secondary safety outcome
251 between both groups (Table 2).

252

253 **Discussion**

254 In the present cohort study, we observed that a DOAC strategy using apixaban or rivaroxaban is
255 prescribed earlier than the guidelines-defined 3 days starting points in a third of patients with

256 acute intermediate-risk PE treated with a DOAC. The rate of outcomes in patients receiving a
257 DOAC earlier after admission was low. Patients in the early group were discharged earlier, with
258 similarly low rates of death and bleeding, and similar RV function recovery compared to the
259 delayed strategy. These results suggest that, if a DOAC is selected by the physician in charge
260 (mainly due to the absence of associated cancer, renal dysfunction, or concomitant antiplatelet
261 therapy), it may be prescribed within the first 72 hours after admission without incurring an
262 excess risk of adverse events. Nevertheless, our results should be interpreted as a pilot study,
263 and deserve confirmation in randomized trials.

264 To the best of our knowledge, our cohort study is the first to describe prescription practices
265 and outcomes in patients with acute intermediate-high risk PE receiving early apixaban or
266 rivaroxaban. The *post hoc* analysis of the HOKUSAI-VTE was currently the only study reporting
267 the effectiveness of the LMWH followed by edoxaban in intermediate-high risk PE as compared
268 to the warfarin regimen [16]. However, most of the information needed to classify the
269 intermediate-high risk PE patients was not available, weakening the interpretation of this study.

270 Thrombolysis is often administered with LMWH [17], and there are some arguments to
271 support the hypothesis that rt-PA could also be used with DOACs. Indeed, apixaban and
272 rivaroxaban share several characteristics with parenteral anticoagulants, such as factor Xa
273 activity, lower risk of major bleeding versus heparin [18], and the lack of a reversal agent [19].
274 Nevertheless, Sharifi et al reported no bleeding in a retrospective study of 159 PE patients
275 treated with low dose rt-PA followed by a DOAC [20]. The ongoing PEITHO-2 trial is
276 investigating whether treatment of intermediate-high risk PE with parenteral heparin over the

277 first 72 hours, followed by dabigatran is effective, but this trial is not designed to evaluate the
278 safety of thrombolysis in PE patients treated with DOAC [21].

279 Our study suffers from several limitations. First, the sample size is relatively small (n = 302),
280 and consequently, may be underpowered to demonstrate a statistical difference in terms of
281 outcomes between the early and delayed DOAC groups. Second, the study design could
282 introduce some selection bias as we focused on intermediate-high risk PE patients treated with
283 a DOAC during the in-hospital course. Indeed, we observed a higher rate of adverse events,
284 especially cancer-related death, in patients who were not treated with a DOAC for
285 intermediate-high risk PE. Patients not treated with a DOAC during the hospital stay were more
286 likely to have active cancer, renal dysfunction and to be treated with concomitant antiplatelet
287 therapy. In this context, prior studies have shown that: (1) cancer-associated VTE patients
288 treated with anticoagulants are at 3-fold higher risk of VTE recurrence, and at 2- to 6-fold
289 higher risk of bleeding [21]; (2) renal dysfunction was an independent predictor of 30-day
290 mortality in PE patients (hazard ratio, 1.6, 95% CI, 1.2-2.1) [22]; and (3) concomitant antiplatelet
291 therapy increased the risk of bleeding in patients treated with an oral anticoagulant [23]. Third,
292 assessment of RV dysfunction on TTE was not centralized in a core laboratory, leading to some
293 potential for misinterpretation of TTE data. Finally, we were unable to identify factors
294 associated with early DOAC prescription despite investigating many confounders in a
295 multivariable model. However, this does not exclude the possibility of hidden confounding. It is
296 likely that the main cause of delay in DOAC prescription was the physician's concern about
297 hemodynamic decompensation or bleeding risk. A previous study showed that a delay in the
298 initiation of oral anticoagulant therapy may be associated with a poor prognosis [22]. Further

299 studies are warranted to better define the profile of patients who may benefit from early DOAC
300 prescription, likely by developing a specific scoring system.

301

302 **Conclusions**

303 In conclusion, the rate of outcomes at 30 days was low in patients receiving a DOAC within 72
304 hours after admission. Patients in the early DOAC group had a shorter length of stay, with
305 similarly low rates of death and bleeding, and similar RV function recovery compared to the
306 delayed strategy. Our results should be interpreted as a pilot study, and deserve confirmation
307 in randomized trials.

308

309 **Figure legends**

310

311 **Figure 1:** Patient flow diagram. PE: pulmonary embolism; DOAC: direct oral anticoagulant;
312 LMWH: low molecular-weight heparin; UFH: unfractionned heparin; VKA: vitamin K agonist.

313

314 **Figure 2:** Bar-diagram of the length of hospital stay according to the anticoagulation regimen at
315 admission: direct oral anticoagulant prescribed with the first 72 hours (early DOAC group) or
316 between 72 hours and discharge (delayed DOAC group). DOAC: direct oral anticoagulant; OR:
317 odds ratio; CI: confidence interval. p-values adjusted for baseline characteristics and
318 antithrombotic therapies

319

320 **Figure 3 :** Assessment of right ventricular recovery as defined by the absolute change in right
321 ventricle-left ventricle diameter ratio (RV/LV) (A), systolic pulmonary artery pressure (sPAP) (B),
322 and tricuspid annulus plane systolic excursion (TAPSE) (C) between transthoracic
323 echocardiography performed at admission and 48 hours later, in intermediate-high risk
324 pulmonary embolism patients (n=209) treated either by early (<72 hours) direct oral
325 anticoagulant or according to the conventional strategy (72 hours or later). p-values adjusted
326 for baseline characteristics and antithrombotic therapies.

327

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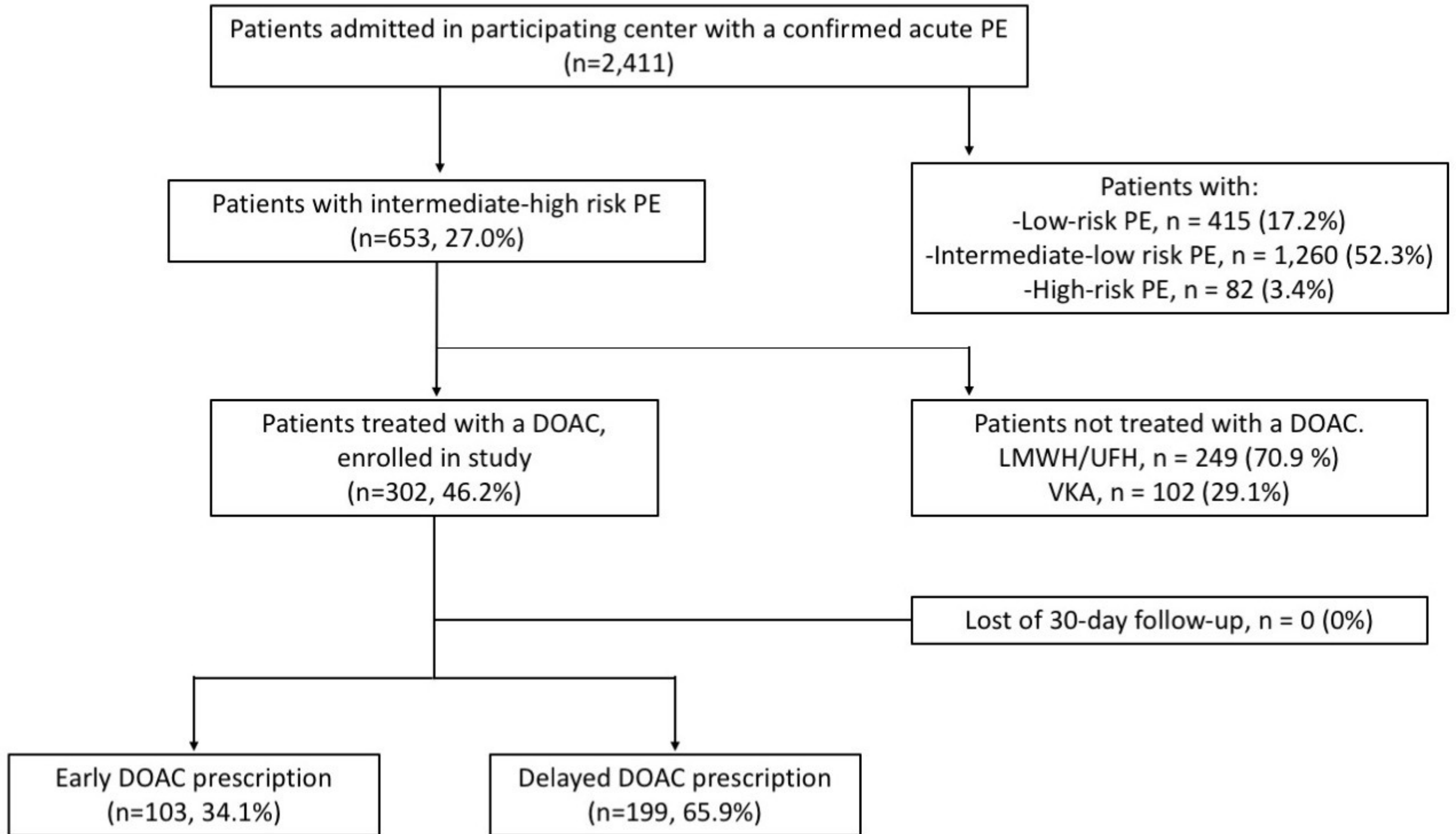
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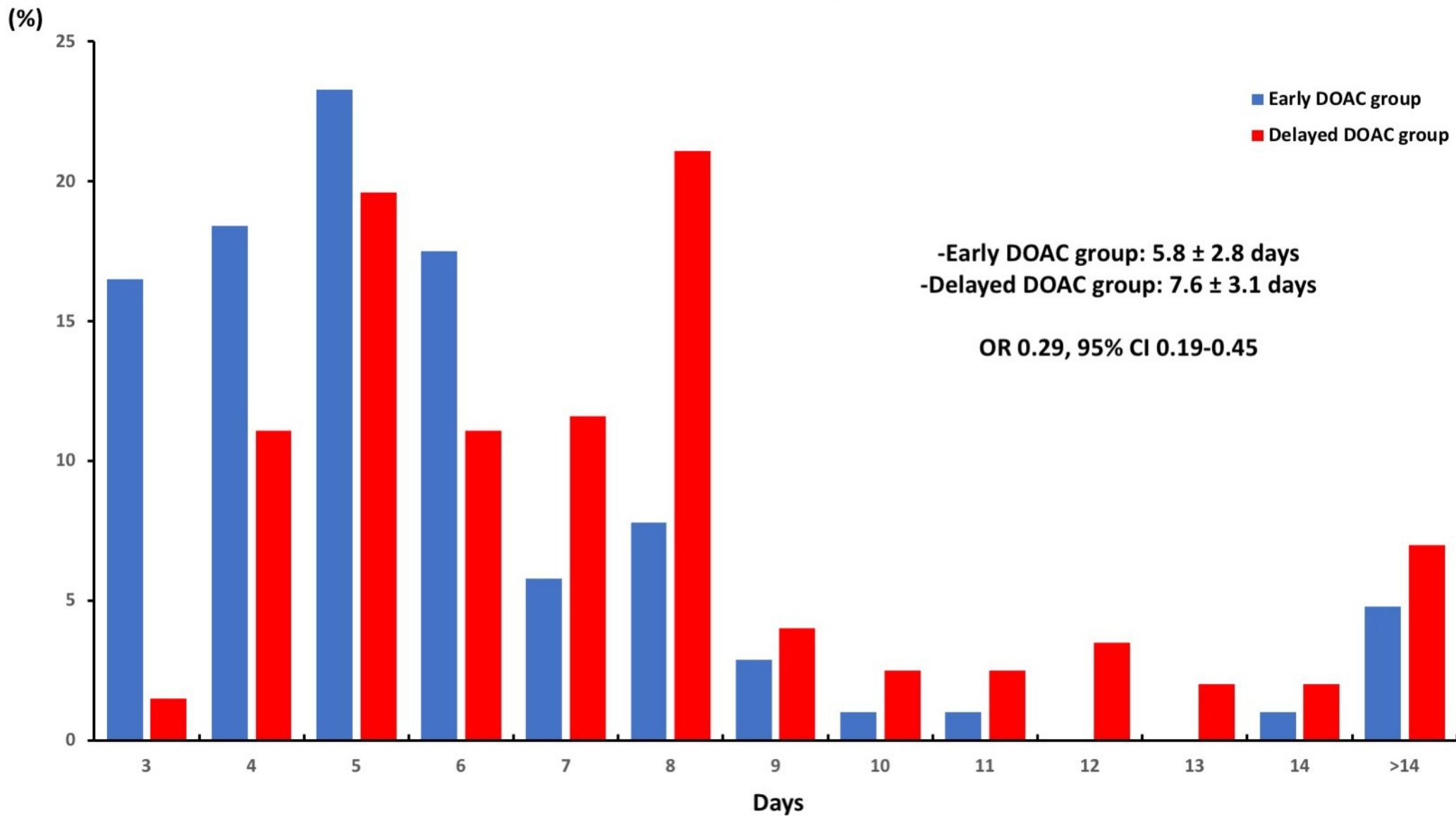
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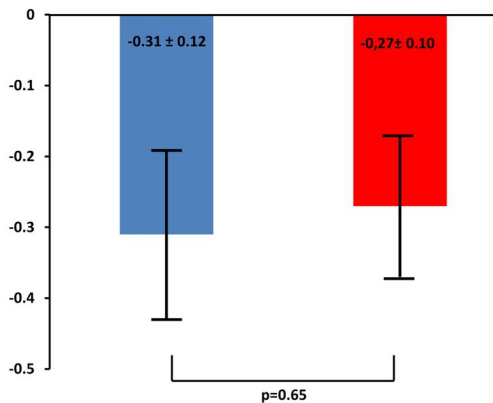
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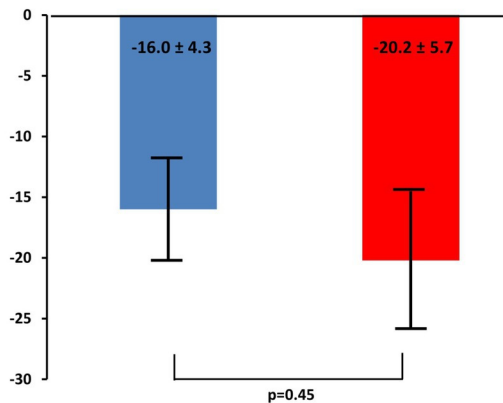
Length of hospital stay



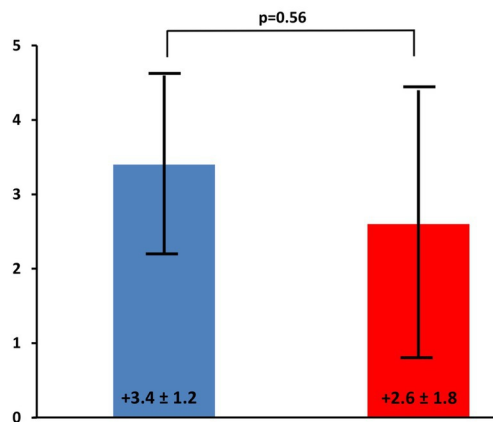
A.

 Δ RV/LV diameter ratio

B.

 Δ sPAP

C.

 Δ TAPSE

■ Early DOAC group

■ Conventional DOAC group

Table 1: Baseline characteristics of the study population according to the prescription of direct oral anticoagulants (i.e., rivaroxaban, or, apixaban) < 72 hours after admission (either without heparin or after a short lead-in period with heparin) (early DOAC group), or at 72 hours or beyond after admission for the treatment of acute intermediate-high risk pulmonary embolism.

Variables	Early DOAC group (n=103)	Delayed DOAC group (n=199)	P-value
Age, years	75.8 ± 16.0	77.3 ± 11.3	0.31
Male (%)	38 (36.9)	77 (38.7)	0.73
BMI	28.1 ± 6.1	27.0 ± 6.3	0.43
Sites of care			0.73
University hospital #1	33 (32.0)	69 (34.7)	
University Hospital #2	25 (24.2)	49 (24.6)	
General hospital #1	12 (11.6)	20 (10.0)	
General hospital #2	10 (9.7)	14 (7.0)	
General hospital #3	10 (9.7)	23 (11.5)	
General hospital #4	7 (6.8)	15 (7.5)	
General hospital #5	6 (5.8)	9 (4.5)	
Co-morbidities (%)			
Diabetes	11 (10.7)	32 (16.1)	0.22
Coronary disease	21 (20.4)	39 (19.6)	0.91
Chronic pulmonary disease	13 (12.6)	32 (16.1)	0.52
Prior vascular disease	30 (29.4)	47 (23.5)	0.10
Active Cancer	1 (1.0)	3 (1.6)	0.88
Neurocognitive disorder	7 (6.8)	5 (2.5)	0.13
Prior VTE	27 (26.2)	40 (20.1)	0.33
Prior bleeding	3 (2.9)	7 (3.5)	0.10
Provoked PE	23 (22.3)	48 (24.1)	0.52
Associated DVT (%)	39 (37.9)	104 (52.3)	0.051

Clinical characteristics (%)			
HR at admission (b.p.m)	91.8 ± 25.9	93.2 ± 23.0	0.72
SBP at admission (mmHg)	140.3 ± 22.3	141.3 ± 25.1	0.80
Arterial oxyhemoglobin saturation (%)	91.2 ± 6.7	90.9 ± 7.5	0.50
Syncope/lightheadedness	15 (14.5)	32 (16.1)	0.30
Biological data (%)			
Hemoglobin (g/dL)	13.2 ± 1.2	13.7 ± 1.6	0.62
Platelet count (x 10 ³ /microliter)	235 ± 73	250 ± 99	0.41
Creatinine clearance (mL/mn)	74.3 ± 49.1	65.6 ± 33.7	0.10
Echo data (%)			
RV/LV ratio	1.05 ± 0.32	0.99 ± 0.18	0.32
sPAP (mmHg)	48.4 ± 12.7	50.2 ± 15.2	0.53
Hypokinesia of free RV wall	33 (32.0)	62 (31.1)	0.82
TAPSE	19.0 ± 4.7	18.5 ± 4.8	0.76
sPESI (points, Q1-Q3)	1.4 ± 0.6	1.5 ± 0.5	0.23
Prior medication usage predisposing to bleeding (i.e. antiplatelet therapy)	19 (18.4)	56 (28.1)	0.07
HAS-BLED	1.65 ± 1.1	1.85 ± 0.96	0.15

DOAC: direct oral anticoagulant; BMI: body mass index; VTE: venous thromboembolic; DVT: deep vein thrombosis; PE: pulmonary embolism; HR: heart rate; SBP: systolic blood pressure; RV: right ventricle; LV: left ventricle; sPAP: systolic pulmonary arterial pressure; TAPSE: Tricuspid annular plane systolic excursion; sPESI: simplified Pulmonary Embolism Severity Index; HAS-BLED: Hypertension-Abnormal renal and liver function-Stroke-Bleeding-Labile INR-Elderly-Drugs or alcohol.

Table 3: Adjusted clinical outcomes according to the prescription of rivaroxaban or apixaban < 72 hours after admission (either without heparin or after a short lead-in period with heparin) (early group), or at 72 hours or beyond after admission for the treatment of acute intermediate-high risk pulmonary embolism.

Clinical outcomes, n (%; 95% CI)		Total	Early DOAC group	Delayed DOAC group	OR (95%CI)
		(n=302)	(n=103)	(n=199)	
Primary efficacy	Death from any cause, or hemodynamic decompensation at 30 days	23 (7.6%; 95% CI, 4.9-11.2)	5 (4.8%; 95% CI, 1.6-10.9)	18 (9.0%; 95% CI, 5.4-13.9)	0.44 (0.15-1.30)
	Death from any cause at 30 days	8 (2.6%; 95% CI, 1.1-5.1)	1 (1.0%; 95% CI, 0.03-5.3)	7 (3.5%; 95% CI, 1.4-7.1)	0.67 (0.32-1.17)
Secondary efficacy	Hemodynamic decompensation at 30 days	15 (4.9%; 95% CI, 2.8-8.0)	4 (3.9%; 95% CI, 1.1-9.7)	11 (5.5%; 95% CI, 2.8-9.6)	0.84 (0.42-1.21)
	Systemic thrombolysis	14 (4.6%; 95% CI, 2.5-7.6)	4 (3.9%; 95% CI, 1.1-9.7)	10 (5.0%; 95% CI, 2.4-9.0)	-
	Surgical embolectomy	1 (0.3%; 95% CI, 0.1-1.8)	0 (0%)	1 (0.5%; 95% CI, 0.1-2.8)	-
	ECMO	0 (0%)	0 (0%)	0 (0%)	-
	PE-related death or hemodynamic decompensation at 30 days	17 (5.6%; 95% CI, 3.3-8.8)	3 (2.9%; 95% CI, 0.6-8.3)	14 (7.0%; 95% CI, 3.9-11.5)	0.60 (0.23-1.13)
	Recurrent VTE at 30 days	4 (1.3%; 95% CI, 0.3-3.3)	1 (1.0%; 95% CI, 0.03-5.3)	3 (1.5%; 95% CI, 0.3-4.3)	0.87 (0.43-1.51)
Primary safety	Major bleeding at 30 days	9 (3.0%; 95% CI, 1.4-5.6)	3 (2.9%; 95% CI, 0.6-8.3)	6 (3.0%; 95% CI, 1.1-6.4)	0.99 (0.45-2.18)

Secondary safety	Intracranial hemorrhage at 30 days	1 (0.3%; 95% CI, 0-0.1)	0 (0)	1 (0.5%; 95% CI, 0-1.5)	-
	Non-major clinically relevant bleeding at 30 days	6 (2.0%; 95% CI, 0.4-7.7)	3 (2.9%; 95% CI, 0.1-6.2)	3 (1.5%; 95% CI, 0.1-8.6)	1.19 (0.33-3.23)

OR: odds ratio; CI: confidence interval; PE: pulmonary embolism; VTE: venous thromboembolism; ECMO: extra-corporeal membrane oxygenation.

Table 3: Unadjusted hazard risk odds ratio for the primary combined efficacy end-point (i.e., all-cause mortality and hemodynamic decompensation) and the primary safety end-point (i.e., major bleeding- at 30-day

Parameters	OR	95% confidence interval	p-value
Primary efficacy outcome			
Male sex	3.61	1.30-10.1	0.01
Age (per quartile)	1.62	1.02-2.57	0.04
Saddle PE	4.62	1.03-20.7	0.04
SBP at admission (per quartile)	1.71	1.08-2.72	0.02
Early DOAC prescription	0.38	0.11-1.38	0.14
Primary safety outcome			
Early DOAC prescription	0.67	0.23-3.76	0.76

PE: pulmonary embolism; SBP: systolic blood pressure; DOAC: direct oral anticoagulant; OR: odds ratio