Contemporary Management and Clinical Course of Acute Pulmonary Embolism: The COPE Study

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Abstract

Background New diagnosis, risk stratification, and treatment strategies became recently available for patients with acute pulmonary embolism (PE) leading to changes in clinical practice and potentially influencing short-term patients' outcomes.

Research question The COntemporary management of PE (COPE) study is aimed at assessing the contemporary clinical management and outcomes in patients with acute symptomatic PE.

Study Design and Methods Prospective, noninterventional, multicenter study. The co-primary study outcomes, in-hospital and 30-day death, were reported overall and by risk categories according to the European Society of Cardiology (ESC) and American Heart Association guidelines.

Results Among 5,213 study patients, PE was confirmed by computed tomography in 96.3%. In-hospital, 289 patients underwent reperfusion (5.5%), 92.1% received parenteral anticoagulants; at discharge, 75.6% received direct oral anticoagulants and 6.7% vitamin K antagonists. In-hospital and 30-day mortalities were 3.4 and 4.8%,

Keywords
- pulmonary embolism
- venous thromboembolism
- anticoagulant
- thrombolysis

* *See Appendix (available in the online version) for the complete list of Centers and Investigators.*
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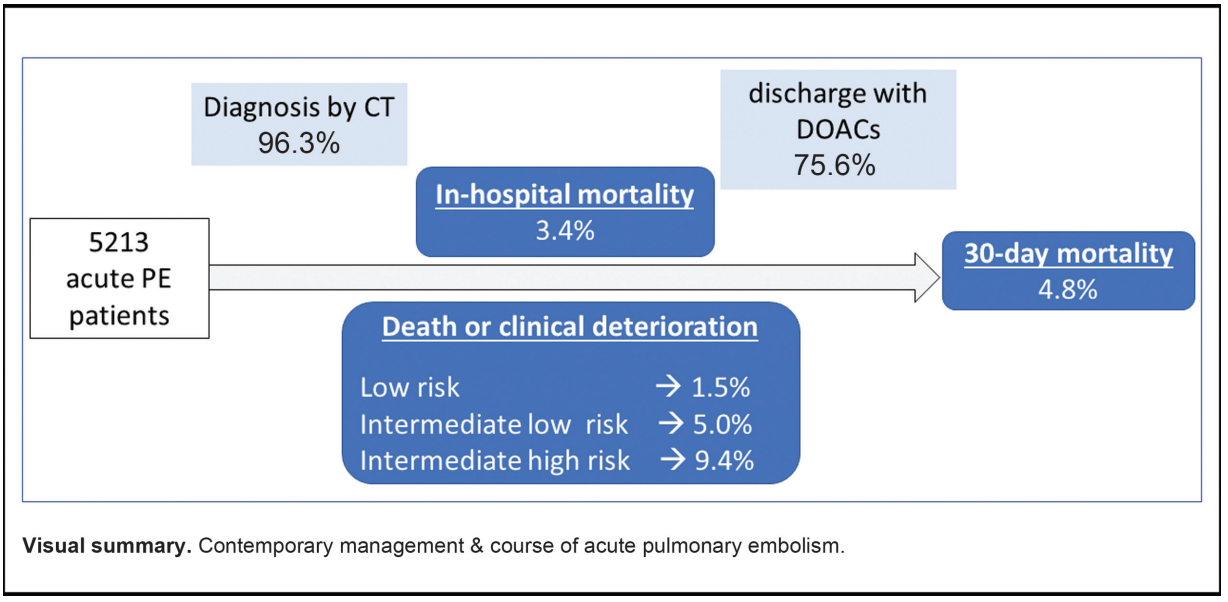

Visual summary. Contemporary management & course of acute pulmonary embolism.

respectively. In-hospital death occurred in 20.3% high-risk patients ($n = 177$), in 4.0% intermediate-risk patients ($n = 3,281$), and in 0.5% low-risk patients ($n = 1,702$) according to ESC guidelines. Further stratification in intermediate-high and intermediate-low risk patients did not reach statistical significance, but intermediate-risk patients with sPESI > 0 alone had lower mortality compared to those with one or both among right ventricular dilation at echocardiography or increased troponin. Death or clinical deterioration occurred in 1.5, 5.0, and 9.4% of patients at low, intermediate-low, and intermediate-high risk for death according to ESC guidelines.

Conclusion For the majority of patients with PE, contemporary initial management includes risk stratification and treatment with direct oral anticoagulants. In-hospital mortality remains high in intermediate and high-risk patients calling for and informing research focused on its reduction.

Trial Registration number: NCT03631810.

Introduction

Acute pulmonary embolism (PE) is a common and potentially fatal disease associated with substantial burden to the health systems.[1–4] The incidence of PE has apparently increased in the last decades, due to improvements in diagnostic pathways and round-the-clock availability of computed tomography (CT) as well as to increased awareness for the disease.[5–7]

Mortality in patients with acute PE varies based on patients' features and severity of disease at presentation.[8] Currently available data on the initial management and early course of the PE in clinical practice rely on studies conducted more than 10 years ago or including both patients with PE and patients with deep vein thrombosis.[9–11] The acute clinical course of PE differs from that of deep vein thrombosis.[12] Moreover, several studies focused on long-term course of PE and reported limited details on the acute phase.[13–16]

In this scenario, international scientific societies endorsed evidence-based management strategies for the management of patients with acute PE.[17–20] Considering the substantial evolution of clinical practice in recent years and the availability of new diagnostic, risk stratification, and treatment strategies, it is crucial to have contemporary data on the management and course of patients with acute PE. Several observational studies exist that describe the management and course of patients with venous thromboembolism, but a minority of these focused in the acute-phase management and course of patients with acute PE.[13–16]

We run a multicenter, prospective, observational study aimed at assessing contemporary management strategies in terms of diagnosis, risk stratification, disposition, treatment,

and the short-term clinical course in patients with acute confirmed PE.

Methods

Study Design

The COntemporary management of PE (COPE; clinicaltrial.gov identifier: NCT03631810) is a prospective, multicenter study of adult patients with acute, symptomatic, objectively diagnosed PE (either first or recurrent episode).[21] Patients were enrolled at cardiology, acute care medicine, and internal medicine departments in Italy. Diagnostic work-out, risk stratification, and treatment strategies were at the discretion and responsibility of the attending physicians.

The study was conducted in accordance with the Declaration of Helsinki and adhered to all applicable national laws and regulations. The study protocol was approved by the Institutional Review Board at the coordinating center and at each site according to local policies.

COPE is an investigator-initiated study. The members of the Steering Committee had fully responsibility for the study design and oversight as well for data analysis and interpretation. The study was supported by an unrestricted grant from Daiichi Sankyo Europe and Daiichi Sankyo Italy. Daiichi Sankyo had no role on study design, data analysis, and interpretation.

Patients

Patients aged 18 years old or older with symptomatic objectively confirmed PE were included in the study after release of informed consent. Criteria for diagnosis of PE have been reported elsewhere.[21]

Patients were excluded in case of participation in controlled trials on the management of acute PE. Patients were evaluated at the time of diagnosis, at discharge, and at 30 days ($\pm$ 4) from the index PE. For patients discharged beyond 30 days from index PE, the study end was considered at 30 days. Follow-up at 30 days was performed by either office visit or phone call.

For the purpose of this study, patients were stratified in risk for death categories as defined by European Society of Cardiology (ESC) guidelines 2014 based on clinical data, imaging, and laboratory results.[19] High-risk patients were those in shock or cardiac arrest at the time of presentation. Low-risk patients were those with a simplified Pulmonary Embolism Severity Index (sPESI) of zero.[19,22] The remaining patients (all with sPESI >0) were categorized at intermediate risk for death and further categorized as (1) intermediate-low risk: one or none among increased troponin or right ventricular dilation (RVD) at echocardiography or (2) intermediate-high risk: increased troponin and RVD at echocardiography. As updated guidelines of the ESC for patients with acute PE were released after this study had started, a further analysis was performed to assess mortality at 30 days in patients stratified according to risk for death categories as defined by ESC guidelines 2019.[19] In these updated guidelines, low-risk patients were defined by sPESI of zero and absence of increased troponin or RVD at echocardiography.

In addition to these prespecified risk stratifications, patients were also stratified, as a post-hoc analysis, according to the strategy supported by the American Heart Association (AHA) as having massive PE (shock or cardiac arrest), submassive PE (hemodynamically stable with RDV at echocardiography or increased troponin or increased brain natriuretic peptide [BNP]/NT-proBNP), or low-risk PE (hemodynamically stable without RDV at echocardiography or increased troponin/BNP/NT-proBNP).[18]

RVD at echocardiography was defined according to local assessment and no central review was planned. Increased troponin was locally defined according to standard cut-off levels of laboratory assays.

Study Outcomes

The co-primary outcomes of the study were in-hospital death and 30-day death. The cause of death was reported by the investigators and documented for central adjudication by an independent Clinical Event Committee unaware of physician classification.[21,23,24]

Death or clinical deterioration was a secondary study outcome.[21]

The safety outcome was major bleeding according to International Society on Thrombosis and Haemostasis criteria, occurring up to 30 days from the index PE.[25]

Statistical Analysis

Data analysis was performed by ANMCO Research Centre of the Heart Care Foundation, Florence, Italy.

Kaplan–Meier estimates were calculated for the occurrence of death at 30 days from the diagnosis of PE in the overall study population and by category of risk according to ESC guidelines 2014.[19] Univariable regression analyses (Cox models) were performed to estimate the risk of in-hospital and 30-day mortality by category of risk according to ESC guidelines 2014, ESC 2019 guidelines, and the AHA guidelines, and reported as hazard ratios (HRs) with 95% confidence interval (CI), and p-values.[18,20]

Multivariable regression analyses (Cox model, backward selection) were performed to identify independent predictors of in-hospital and 30-day all-cause death. Multivariable analyses were constructed from the set of significant ($p < 0.10$) univariable predictors at entry and of covariates of clinical interest (see legend of ►**Table 5**). Gender was added to multivariable models as variable of clinical interest. Three models were performed, the first with clinical variables only, the second with clinical, instrumental, and laboratory variables, and the third including thrombolytic and anticoagulant therapies. Instrumental examinations and laboratory parameters were considered obtained at entry only if performed between 24 hours before and 48 hours following the PE diagnosis. Multivariable regression analyses were also performed to identify predictors of clinical deterioration and of the combined end-point all-cause death or clinical deterioration during hospital stay.

Analyses were performed with SAS system software, version 9.4.

Results

One hundred-eighty-two centers participated in the study, 63 internal medicine, 75 cardiology, and 44 acute care departments. The first patient was included on March 15, 2018, and recruitment was concluded on December 31, 2020. The end of last patient follow-up was on January 31, 2021.

Overall, 5,213 patients were included in the study (►**Supplementary Fig. S1**, available in the online version); follow-up at 30 days was available in 5,203 patients (99.8%; 10 patients lost to 30-day follow-up). The mean age of study patients was 70 ± 16 years, with 12.7% being 50 years old or younger and 28.9% older than 80 years (►**Supplementary Fig. S2**, available in the online version). Main features of study patients are reported in ►**Table 1**.

Active cancer was reported in 832 patients (16.8%), while 699 patients had a history of cancer (13.4%). Surgery or trauma was reported in less than 10% each, while the prevalence of bed rest longer than 3 days in the previous 4 weeks was 21.9%. In 94 patients, COVID-19 (coronavirus disease 2019) infection was present at time of PE.

The prevalence of symptoms at diagnosis is reported in ►**Supplementary Table S1** (available in the online version). Of note, hemoptoe was reported in 2% of the patients at diagnosis.

Diagnosis of PE

At admission, 1,466 patients were classified as having high (28%), 2,524 intermediate (48%), and 1,223 low pretest probability for PE (24%) as assessed implicitly by the attending physician or by the use of validated scores. Pretest probability of PE in patients admitted for PE or diagnosed with acute symptomatic PE while admitted for other causes is reported in ►**Supplementary Table S2** (available in the online version).

Diagnostic tests are reported in ►**Table 2**. D-dimer was assessed in 78% of the patients and was found to be increased in 98%; of note, D-dimer was apparently obtained regardless of pretest clinical probability (74% of patients with high pretest clinical probability).

PE was confirmed by CT angiography in 5,020 patients (96.3%), by perfusion lung scan in 72 patients (1.4%), and by a combination of lower limb ultrasonography and/or echocardiography and pretest clinical probability in 111 patients (2.1%). A concomitant deep vein thrombosis was diagnosed in about 60% of the patients in whom ultrasonography of the lower limbs was performed (►**Table 2**).

More than 80% of patients had at least one test for death risk stratification during the hospital stay. These tests were obtained within 48 hours after diagnosis of index PE in 64, 78, and 51% patients for echocardiography, troponin, and BNP/NT-proBNP, respectively.

Treatment

In-hospital, 5,158 (99%) patients received anticoagulant treatment. During the hospital stay, 5.5% received reperfusion therapy. At discharge, 75.6 and 6.7% of patients received a direct oral anticoagulant (DOAC) or a vitamin K antagonist (VKA), respectively (►**Table 3**).

Table 1 Main characteristics of study patients

	Total population (*n* = 5,213)
Age (y), mean ± SD	70 ± 16
Range	18–100
< 65, *n* (%)	1,618 (31.0)
> 80, *n* (%)	1,508 (28.9)
Male sex, *n* (%)	2,485 (47.7)
Risk factors for VTE	
Previous VTE, *n* (%)	883 (16.9)
Cancer, active[a] (4,950 patients)[b], *n* (%)	832 (16.8)
Cancer, history, *n* (%)	699 (13.4)
Surgery <4 wk, *n* (%)	346 (6.6)
Trauma <4 wk, *n* (%)	380 (7.3)
Major trauma <4 wk, *n* (%)	94 (1.8)
Bed rest >3 days <4 wk (5,074 patients)[b], *n* (%)	1,112 (21.9)
Hospitalization <4 wk, *n* (%)	713 (13.7)
Hormonal treatment, *n* (%) *on 2,728 females*	204 (7.5)
Pregnancy, *n* (%) *on 2,728 females*	23 (0.8)
Comorbidities	
COPD, *n* (%)	652 (12.5)
CHF, *n* (%)	368 (7.1)
Hemodialysis, *n* (%)	17 (0.3)
Cirrhosis, *n* (%)	45 (0.9)
Cognitive impairment, *n* (%)	526 (10.1)
Obesity (5,042 patients)[b], *n* (%)	1,066 (21.1)
Major bleeding <4 wk, *n* (%)	76 (1.5)
HIT (5,079 patients)[b], *n* (%)	9 (0.2)

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HIT, heparin-induced thrombocytopenia; VTE, venous thromboembolism.
[a]Active cancer defined as diagnosis within 6 months or on ongoing anticancer treatment or metastatic.
[b]Percentages were evaluated on patients with data available, reported in brackets for each variable.

Management and Course

Out of 4,885 patients admitted to the emergency department due to acute PE, 1.2% were discharged from the emergency department, 5.8% were managed by early discharge (usually within 48 hours), and 93.0% by standard hospitalization (1,475 at cardiology, 1,177 internal medicine, 1,276 acute care, and 612 other departments). The median duration of hospitalization was 7 days (interquartile range: 5–12 days). Among 59 patients discharged from the emergency department, 24 (40.7%) had low risk and 23 (39.0%) intermediate-low risk PE; among 286 patients managed by early discharge, 116 (40.6%) had low risk and 104 (36.4%) intermediate-low risk PE.

Table 2 Test performed in the total population and according to the pretest clinical probability

Test performed	Total population ($n = 5,213$)	Pretest clinical probability		
		High ($n = 1,466$)	Intermediate ($n = 2,524$)	Low ($n = 1,223$)
Initial tests				
D-dimer, *n* (%)	4,044 (77.6)	1,083 (73.9)	1,995 (79.0)	966 (79.0)
Increased, n (%)	*3,962 (98.0)*	*1,070 (98.8)*	*1,952 (97.8)*	*940 (97.3)*
Chest X-ray, *n* (%)	2,852 (54.7)	707 (48.2)	1,397 (55.4)	748 (61.2)
Abnormal, n (%)	*1,414 (49.6)*	*354 (50.1)*	*705 (50.5)*	*355 (47.5)*
EKG, *n* (%)	5,056 (97.0)	1,433 (97.8)	2,442 (96.8)	1,181 (96.6)
Blood gas analysis, *n* (%)	4,293 (82.4)	1,269 (86.6)	2,072 (82.1)	952 (77.8)
Imaging				
CT angiography, *n* (%)	5,031 (96.5)	1,406 (95.9)	2,441 (96.7)	1,184 (96.8)
Positive for PE, n (%)	*5,020 (99.8)*	*1,403 (99.8)*	*2,436 (99.8)*	*1,181 (99.8)*
More proximal localization of emboli:				
Main pulmonary arteries, n (%)	*2,207 (44.0)*	*715 (51.0)*	*1,113 (45.7)*	*379 (32.1)*
Segmental, n (%)	*1,327 (26.4)*	*284 (20.2)*	*626 (25.7)*	*417 (35.3)*
Isolated subsegmental, n (%)	*220 (4.4)*	*33 (2.4)*	*111 (4.6)*	*76 (6.4)*
Bilateral emboli, n (%)	*1,266 (25.2)*	*371 (26.4)*	*586 (24.1)*	*309 (26.2)*
CT assessment of the RV, n (%)	*571 (11.4)*	*175 (12.5)*	*271 (11.1)*	*125 (10.6)*
Perfusion lung scan, *n* (%)	84 (1.6)	8 (0.6)	51 (2.0)	25 (2.0)
NMR, *n* (%)	6 (0.1)	3 (0.2)	2 (0.1)	1 (0.1)
Pulmonary angiography, *n* (%)	21 (0.4)	12 (0.8)	5 (0.2)	4 (0.3)
Lower limb ultrasonography, *n* (%)	4,108 (78.8)	1,173 (80.0)	1,949 (77.2)	986 (80.1)
Positive for DVT, n (%)	*2,507 (61.0)*	*861 (73.4)*	*1,208 (62.0)*	*438 (44.4)*
More proximal localization:				
Inferior vena cava, n (%)	*28 (1.1)*	*10 (1.2)*	*12 (1.0)*	*6 (1.4)*
Isolated distal, n (%)	*323 (12.9)*	*63 (7.3)*	*172 (14.2)*	*88 (20.1)*
Echocardiography, *n* (%)	4,229 (81.1)[a]	1,208 (82.4)	2,048 (81.1)	973 (79.6)
Abnormal[b]*, n (%)*	2,578 (61.0)	817 (67.6)	1,285 (62.7)	476 (48.9)

Abbreviations: CT, computed tomography; DVT, deep vein thrombosis; EKG, electrocardiogram; PE, pulmonary embolism; NMR, nuclear magnetic resonance.

[a]Echocardiography was obtained within 24 hours from admission in 2,152 patients (41%) and within 48 hours from admission in 3,330 patients (64%).

[b]RVD defined as presence of one among RV dilation, RV hypokinesis, interventricular septum paradoxical motion, pulmonary hypertension, reduced tricuspid annulus plane systolic excursion, or mobile emboli.

The overall crude in-hospital mortality was 3.4%; the main cause for in-hospital death was PE (49%) (►**Fig. 1**). The Kaplan–Meier curve for time to all-cause death is reported in ►**Fig. 2A**. Mortality at 30 days was 4.8%; for main causes, see ►**Fig. 1**.

Death or clinical deterioration occurred in 293 patients during the hospital stay (5.6%), in 214 of them (73%) within 7 days from diagnosis of PE.

Major bleeding rate was 2.6% during the hospital stay and 2.9% at 30 days.

Mortality: Role of Risk Stratification

After categorization of the patients by risk of death according to the ESC guidelines 2014, in-hospital death occurred in 20.3% of 177 high-risk patients (HR: 28.1, 95% CI: 13.0–60.6), in 4.0% of the 3,281 intermediate-risk (HR: 6.4, 95% CI: 3.1–13.0), and in 0.5% of 1,702 low-risk patients; death at 30 days occurred in 22.6% high-risk (HR: 51.7, 95% CI: 25.1–106.5), 6.0% intermediate-risk (HR: 11.7, 95% CI: 6.0–22.8), and 0.5% low-risk patients, respectively (►**Table 4**). Kaplan–Meier curves for time to death in patients at low, intermediate, and high risks for death are reported in ►**Fig. 2B**. The risk for death at 30 days was higher in all subgroups of patients at intermediate risk, namely those with increased troponin or RVD at echocardiography and increased troponin plus RVD at echocardiography, in comparison to patients at low risk for death (►**Table 4**).

Among intermediate-risk patients, the subgroup of those with sPESI > 0, no RVD, and normal troponin (intermediate

Table 3 Anticoagulant treatment during hospital stay and at discharge

Anticoagulant treatment during hospital stay	Total population ($n = 5,213$)	Anticoagulant treatment at discharge	Patients discharged alive within 30 days ($n = 4,786$)
UFH, *n* (%)	1,228 (23.6)	UFH, *n* (%)	20 (0.4)
LMWH, *n* (%)	2,758 (52.9)	LMWH, *n* (%)	567 (11.9)
Fondaparinux, *n* (%)	1,424 (27.3)	Fondaparinux, *n* (%)	320 (6.7)
At least 1 parenteral anticoagulant, n (%)	*4,801 (92.1)*	*At least 1 parenteral anticoagulant, n (%)*	*906 (18.9)*
VKAs	280 (5.4)	VKAs	319 (6.7)
DOACs	2,597 (49.8)	DOACs	3,617 (75.6)
At least 1 oral anticoagulant, n (%)	*2,860 (54.9)*	*At least 1 oral anticoagulant, n (%)*	*3,936 (82.2)*
At least 1 anticoagulant, n (%)	*5,158 (98.9)*	*At least 1 anticoagulant, n (%)*	*4,748 (99.2)*
Contraindication for AC, *n* (%)	105 (2.0)	–	
Vena cava filter, *n* (%)	51 (1.0)	Vena cava filter, *n* (%)	22 (0.5)

Abbreviations: AC, anticoagulation; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist.

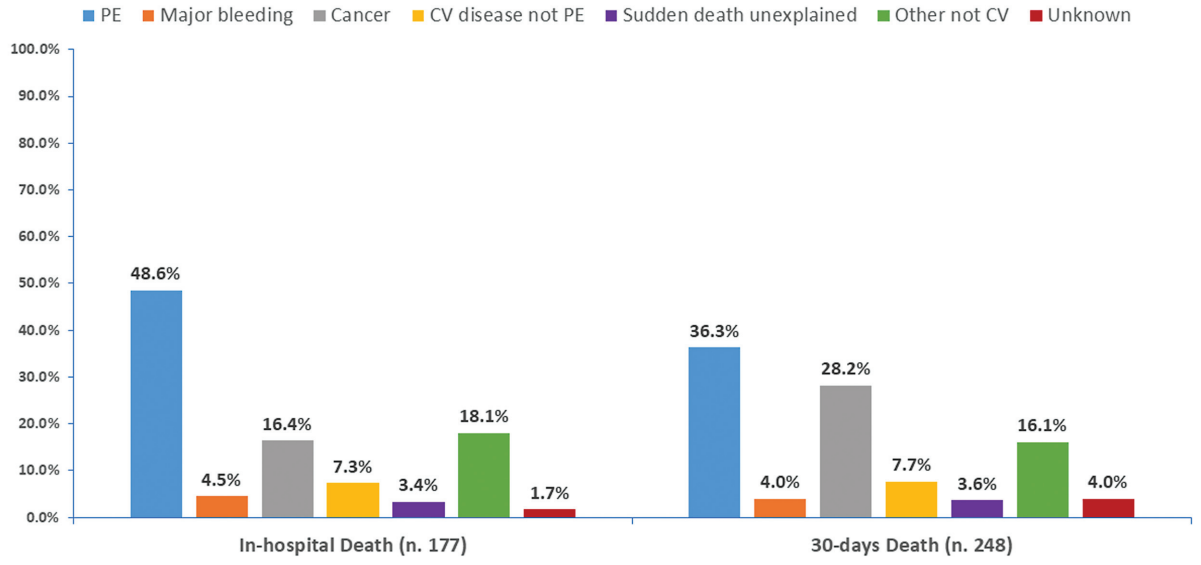

Fig. 1 Cause of death during the hospital stay and at 30 days

very low risk) had significantly lower mortality at 30 days compared to those with sPESI >0 and one among RVD or increased troponin and numerically but not significantly lower compared to intermediate-high risk patients (sPESI > 0, RVD, and increased troponin) (►**Table 4**, ►**Fig. 2C**). No difference emerged between intermediate-low and intermediate-high risk patients.

Of note, sPESI classified 65% of patients younger than 50 years and 28% of those aged 50 or older at low risk for death (396 out of 607 and 1,306 out of 4,606, respectively). The negative predictive value of sPESI = 0 for death at 30 days was 99.7% (95% CI: 99.2–100%) and 99.4% (95% CI: 99.0–99.8%) in the two age groups, respectively. The positive predictive value of sPESI > 0 for death at 30 days was 4.3% (95% CI: 1.5–7.0%) and 6.9% (95% CI: 6.1–7.8%) in the two age groups, respectively.

When the ESC 2019 strategy for risk stratification was used, patients at low risk for death reduced to 912 (17.5% of the study population) and 790 patients were upgraded from low to intermediate-risk category. Low risk patients according to the ESC 2019 strategy had in-hospital mortality of 0.2% and 30-day mortality of 0.3% (►**Table 4**). All subgroups of intermediate-risk patients and high-risk patients had increased risk for death either in-hospital or at 30 days in comparison to those at low risk (►**Table 4**). Among intermediate-risk patients, the subgroup with sPESI > 0, no RVD, and normal troponin had significantly lower in-hospital mortality compared to those with sPESI > 0, and one among RVD or increased troponin and to those with sPESI > 0, RVD, and increased troponin (intermediate-high risk patients) (►**Table 4**). No difference emerged among these patient subgroups with

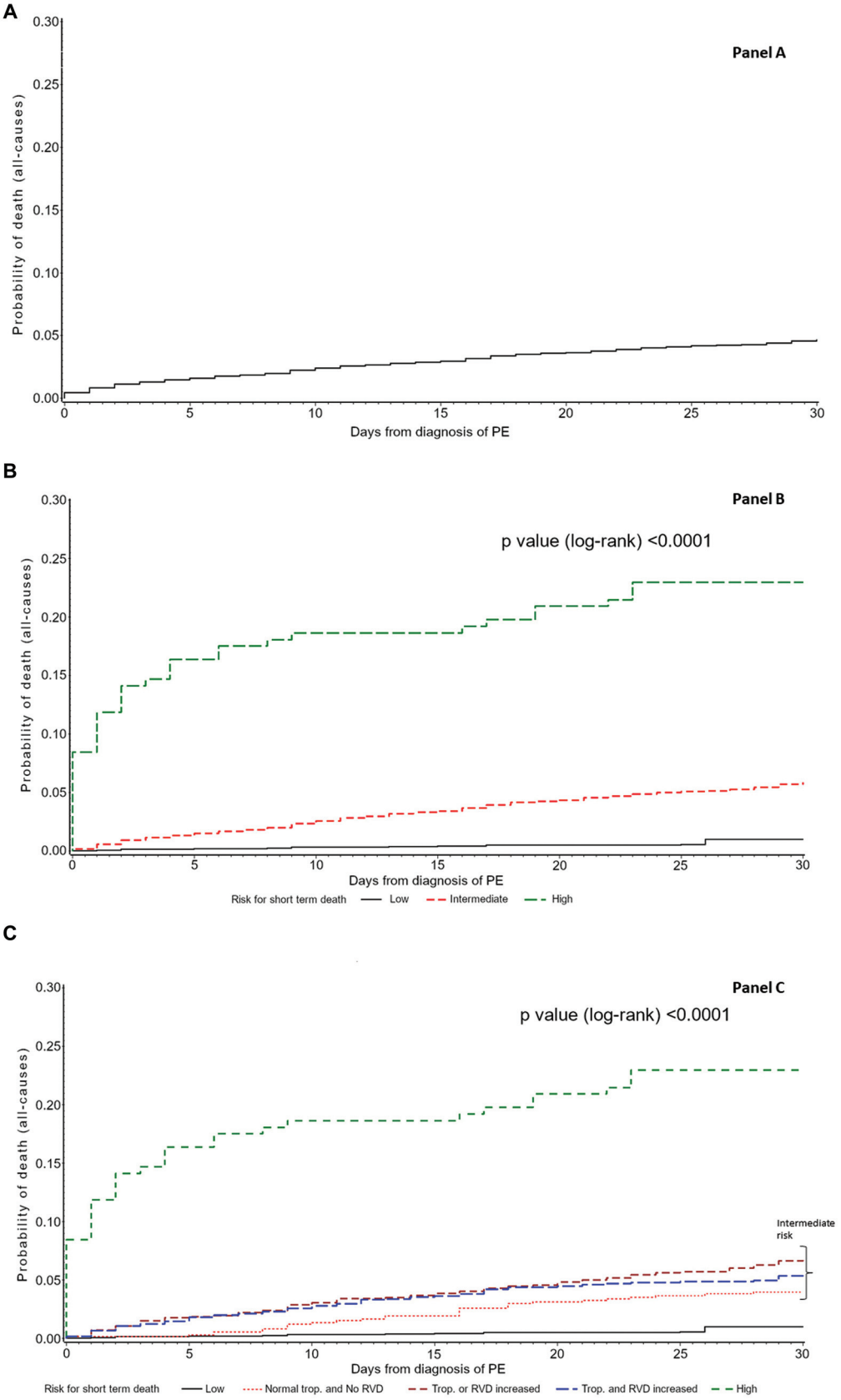

Fig. 2 Kaplan–Meier curve for time to all-cause death: in the overall study population (**A**); by category of risk according to ESC guidelines 2014 (**B**); and with further categorization of intermediate-risk patients (**C**).

Table 4 Unadjusted risk estimates for in-hospital and 30-day mortality by risk category according to different risk categories for death in-hospital and at 30 days

	In-hospital death				30-day death			
	N (%)	HR	95% CI	*p*	*N* (%)	HR	95% CI	*p*
ESC 2014								
Low risk (sPESI = 0), *n* = 1,702	8 (0.5)	1	–	–	9 (0.5)	1	–	–
Intermediate risk (sPESI ≥ 1), *n* = 3281	132 (4.0)	6.35	3.1–13.0	< 0.0001	198 (6.0)	11.71	6.0–22.8	< 0.0001
High risk (shock or cardiac arrest), *n* = 177	36 (20.3)	28.08	13.0–60.6	< 0.0001	40 (22.6)	51.67	25.1–106.5	< 0.0001
Unknown risk, *n* = 53	1 (1.9)	4.26	0.5–34.1	0.17	1 (1.9)	3.63	0.5–28.7	0.22
ESC 2014 with stratification of intermediate-risk patients								
Low risk (sPESI = 0), *n* = 1,702	8 (0.5)	1	–	–	9 (0.5)	1	–	–
Intermediate low risk, *n* = 1,857	66 (3.6)	5.7	2.7–11.9	< 0.0001	112 (6.0)	11.7	5.9–23.0	< 0.0001
sPESI > 0, no RVD, normal troponin, n = 740	*14 (1.9)*	*3.13*	*1.3–7.5*	*0.0102*	*31 (4.2)*	*8.05*	*3.8–16.9*	*< 0.0001*
sPESI > 0, RVD or increased troponin, n = 1,117	*52 (4.7)*	*7.35*	*3.5–15.5*	*< 0.0001*	*81 (7.3)*	*14.11*	*7.1–28.1*	*< 0.0001*
Intermediate high risk, *n* = 1,210	*52 (4.3)*	6.66	3.2–14.0	< 0.0001	*65 (5.4)*	10.41	5.2–20.9	< 0.0001
Intermediate unknown risk, *n* = 214	*14 (6.5)*	9.94	4.2–23.7	< 0.0001	*21 (9.8)*	19.44	8.9–42.4	< 0.0001
High risk (shock or cardiac arrest), *n* = 177	36 (20.3)	28.10	13.0–60.7	< 0.0001	40 (22.6)	51.66	25.1–106.4	< 0.0001
Unknown risk, *n* = 53	1 (1.9)	4.26	0.5–34.1	0.17	1 (1.9)	3.63	0.5–28.6	0.22
ESC 2019								
Low risk (sPESI = 0), *n* = 912	*2 (0.2)*	1	–	–	3 (0.3)	1	–	–
Intermediate risk (sPESI ≥ 1), *n* = 4,103	*139 (3.4)*	10.79	2.7–43.6	0.0008	205 (5.0)	15.51	5.0–48.5	< 0.0001
High risk (shock or cardiac arrest), *n* = 177	*36 (20.3)*	54.29	13.0–226.1	< 0.0001	40 (22.6)	83.06	25.7–268.5	< 0.0001
Unknown risk, *n* = 21	*0*	0.0	0.0–.	0.98	0	0.0	$0.0–8.9^{*}10^{261}$	0.98
ESC 2019 with stratification of intermediate-risk patients								
Low risk (sPESI = 0), *n* = 912	2 (0.2)	1	–	–	3 (0.3)	1	–	–
Intermediate low risk, *n* = 2,342	69 (2.9)	9.6	2.4–39.4	0.002	115 (4.9)	15.2	4.8–47.9	< 0.0001
sPESI > 0, no RVD, normal troponin, n = 740	*14 (1.9)*	*6.07*	*1.4–26.7*	*0.0172*	*31 (4.2)*	*12.95*	*4.0–42.4*	*< 0.0001*
sPESI > 0, RVD or increased troponin, n = 1,602	*55 (3.4)*	*11.33*	*2.8–46.5*	*0.0008*	*84 (5.2)*	*16.26*	*5.1–51.4*	*< 0.0001*
Intermediate high risk, *n* = 1,547	*56 (3.6)*	11.23	2.74–46.06	0.0008	*69 (4.5)*	13.84	4.36–43.97	< 0.0001
Intermediate unknown risk, *n* = 214	*14 (6.5)*	19.26	4.37–84.87	< 0.0001	*21 (9.8)*	31.26	9.32–104.79	< 0.0001
High risk (shock or cardiac arrest), *n* = 177	36 (20.3)	54.30	13.04–226.13	< 0.0001	40 (22.6)	83.07	25.70–268.53	< 0.0001
Unknown risk, *n* = 21	0	0.0	0.0–	0.98	0	0.0	$0.0–4.56^{*}10^{262}$	0.98

Table 4 (*Continued*)

	In-hospital death				30-day death			
	N (%)	HR	95% CI	*p*	*N* (%)	HR	95% CI	*p*
AHA								
Low risk, $n = 1{,}384$	12 (0.9)	1	–	–	24 (1.7)	1	–	–
Submassive PE, $n = 3{,}391$	116 (3.4)	3.21	1.77–5.81	0.0001	165 (4.9)	2.85	1.86–4.37	<0.0001
Massive PE, $n = 177$	36 (20.3)	15.86	8.23–30.56	<0.0001	40 (22.6)	15.68	9.45–26.01	<0.0001
Unknown risk, $n = 261$	13 (5.0)	4.87	2.22–10.69	<0.0001	19 (7.3)	4.32	2.37–7.89	<0.0001

Abbreviations: AHA, American Heart Association; CI, confidence interval; ESC, European Society of Cardiology; HR, hazard ratio; PE, pulmonary embolism; RVD, right ventricular dilation; sPESI, simplified Pulmonary Embolism Severity Index.

respect to mortality at 30 days. The features of the 790 patients categorized at low risk according to the 2014 ESC guidelines and at intermediate risk according to the 2019 guidelines are reported in ►**Supplementary Table S3** (available in the online version). Of note, mortality during the hospital stay and at 30 days in these 790 patients was 0.8%.

By using the pragmatic AHA strategy, hemodynamically stable patients were divided in submassive ($n = 3{,}391$) and low risk ($n = 1{,}384$). In-hospital death occurred in 3.4 and 0.9% of these patients, respectively, and death at 30 days in 4.9 and 1.7%, respectively.

Noteworthy, 30 (3.8%) of these patients received thrombolytic therapy during the hospital stay.

In about 5.0% of patients at intermediate risk for death/submassive PE, troponin and echocardiography were not obtained. Mortality was particularly high in these patients.

Predictors of Death and Clinical Deterioration

Multiple-regression modelling identified nine clinical variables as independent risk factors for in-hospital death (►**Table 5**). Among laboratory and instrumental findings within 48 hours from diagnosis of PE, increased troponin and anemia were predictors of in-hospital death. RVD was an independent predictor of in-hospital death when it was considered regardless of the timing of assessment during the hospital stay (RVD present vs. absent: HR: 1.93, 95% CI: 1.15–3.23; not performed vs. RVD absent: HR: 2.56, 95% CI: 1.48–4.44). Of importance, RVD at echocardiography performed within 48 hours from diagnosis of PE was not associated with increased risk for death. Similar results were obtained for BNP/NT-pro at entry.

Of note, when treatments were included to the multivariable models, thrombolytic treatment was associated with death during the hospital stay and at 30 days (HR: 1.60, 95% CI: 1.02–2.53; HR: 1.99, 95% CI: 1.32–3.01); anticoagulant treatment was associated with reduced risk for death during the hospital stay and at 30 days.

All the clinical predictors for in-hospital death were confirmed to be predictors of death at 30 days, with the addition to history of heart failure, cognitive impairment, and respiratory rate of 30 breaths per minute or more. Of note, anemia and increased BNP or NT pro-BNP levels within 48 hours from admission were associated with 30-day mortality (►**Table 5**).

Patients experiencing clinical deterioration during hospital stay were more commonly hypotensive (systolic blood pressure lower than 100 mmHg), tachypneic (respiratory rate >20 breaths per minute), with RVD at echocardiography or increased troponin in comparison to patients discharged alive without having clinical deterioration (►**Supplementary Table S4**, available in the online version>). Clinical deterioration occurred in 1.2, 3.1, and 7.6% of patients at low, intermediate low, and intermediate high risk for death at hospital admission, according to ESC 2014 strategy. Death or clinical deterioration occurred in 1.5, 5.0, and 9.4% of patients at low, intermediate low, and intermediate high risk for death according to the ESC 2014 strategy. Independent predictors for in-hospital clinical deterioration and for death or clinical

Table 5 Predictors of death in-hospital and at 30 days as assessed by Cox proportional hazard models (backward selection)

Variables	*In-hospital*		*30 days*	
	Model I *Clinical variables* *p* *HR [95% CI]*	*Model II* *Clinical and instrumental variables* *p* *HR [95% CI]*	*Model I* *Clinical variables* *p* *HR [95% CI]*	*Model II* *Clinical and instrumental variables* *p* *HR [95% CI]*
Clinical variables				
Age, y	<0.0001 1.03 [1.02–1.04]	0.0002 1.03 [1.01–1.04]	<0.0001 1.03 [1.02–1.04]	<0.0001 1.03 [1.01–1.04]
Female gender	NS	NS	NS	NS
Systolic blood pressure, mmHg	0.0011 0.989 [0.983–0.996]	0.0030 0.990 [0.983–0.997]	0.0064 0.992 [0.987–0.998]	0.0288 0.994 [0.988–0.999]
Heart rate, beats per min	0.0014 1.007 [1.003–1.012]	0.0020 1.007 [1.003–1.012]	<0.0001 1.009 [1.005–1.013]	<0.0001 1.010 [1.006–1.014]
Respiratory rate[a], breaths per min 20–29 vs. <20 ≥30 vs. <20 Unknown vs. <20	0.042 1.20 [0.79–1.84] 2.02 [1.22–3.34] 1.39 [0.91–2.11]	NS	0.0031 1.14 [0.80–1.61] 2.02 [1.31–3.12] 1.53 [1.09–2.14]	0.009 1.13 [0.80–1.61] 1.98 [1.28–3.08] 1.42 [1.01–2.00]
Reduced urinary output[b] Yes vs. no Not assessed vs. no	0.0002 2.32 [1.55–3.47] 1.15 [0.72–1.82]	0.0001 2.35 [1.57–3.51] 1.17 [0.73–1.86]	<0.0001 2.42 [1.69–3.48] 1.03 [0.69–1.56]	<0.0001 2.39 [1.66–3.44] 1.10 [0.74–1.66]
Abnormal vigilance status due to PE Yes vs. no	0.0244 1.62 [1.06–2.46]	0.0125 1.70 [1.12–2.58]	0.0117 1.64 [1.12–1.56]	0.0108 1.64 [1.12–2.40]
Active cancer[c] Yes vs. no Unknown vs. no	<0.0001 3.40 [2.47–4.68] 1.44 [0.80–2.60]	<0.0001 3.23 [2.34–4.48] 1.51 [0.83–2.73]	<0.0001 5.66 [4.36–7.36] 1.56 [0.92–2.65]	<0.0001 5.30 [4.05–6.94] 1.62 [0.95–2.77]
> 3 days in bed ≤4 wk prior to PE[d] Yes vs. no Unknown vs. no	0.0058 1.55 [1.13–2.14] 2.11 [1.14–3.90]	0.0048 1.55 [1.12–2.13] 2.19 [1.18–4.06]	0.0002 1.67 [1.26–2.20] 2.23 [1.30–3.84]	0.0009 1.56 [1.19–2.06] 2.13 [1.23–3.70]
COPD Yes vs. no	0.0003 1.90 [1.34–2.69]	0.0002 1.94 [1.37–2.76]	0.0087 1.54 [1.12–2.13]	0.0078 1.55 [1.12–2.14]
Heart failure Yes vs. no	NS	NS	0.0147 1.58 [1.10–2.29]	0.0238 1.54 [1.06–2.30]
Cognitive impairment Yes vs. no	NS	NS	0.0363 1.43 [1.02–2.00]	0.0245 1.46 [1.05–2.04]
Hospitalization ≤4 wk prior to PE	NS	NS	NS	NS
Previous VTE	NS	NS	NS	NS
Abnormal saturation	NS	NS	NS	NS
Instrumental variables				
ECG at entry[e] RV overload vs. no RV overload Not performed vs. no RV overload	–	0.0453 0.97 [0.69–1.38] 1.99 [1.13–3.48]	–	0.0333 0.95 [0.71–1.28] 1.86 [1.14–3.05]
Echocardiography at entry[f] RVD vs. no RVD Not performed vs. no RVD	–	NS	–	NS
Troponin at entry[g] Increased vs. normal Not performed vs. normal	–	0.0193 1.97 [1.21–3.22] 1.95 [1.13–3.37]	–	NS
BNP/NT-pro at entry[h] Increased vs. normal Not assessed vs. normal	–	NS	–	0.0282 2.08 [1.22–3.56] 1.88 [1.10–3.20]

Table 5 (*Continued*)

Variables	*In-hospital*		*30 days*	
	Model I Clinical variables p HR [95% CI]	*Model II Clinical and instrumental variables p HR [95% CI]*	*Model I Clinical variables p HR [95% CI]*	*Model II Clinical and instrumental variables p HR [95% CI]*
Hemoglobin at entry[i], g/dL ≤10 vs. >13 >10–13 vs. >13 Unknown vs. >13	–	0.0167 1.11 [0.66–1.86] 1.52 [1.07–2.18] 0.63 [0.29–1.36]	–	<0.0001 2.06 [1.37–3.08] 1.81 [1.32–2.46] 0.76 [0.39–1.48]
Creatinine clearance at entry[j], mL/min <30 vs. >60 30–60 vs. >60 Unknown vs. >60	–	NS	–	NS

Abbreviations: CI, confidence interval; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; HR, hazard ratio; RV, right ventricle; RVD, right ventricular dysfunction; VTE, venous thromboembolism.
Note: Age, systolic blood pressure, and heart rate are considered as continuous variables.
The following variables were inserted in the Cox models (when more than two categories were present, dummy variables were introduced to define a reference group [RG]):
Clinical: age (continuous), systolic blood pressure (continuous), and heart rate (continuous), gender, previous VTE, active cancer (yes, no (RG), unknown), bed rest >3 days <4 weeks prior of EP (yes, no (RG), unknown), hospitalization <4 weeks prior of EP, COPD, CHF, cognitive impairment, altered saturation (oxygen saturation <90% in room air or <95% with oxygen), respiratory rate (≥30, 29–20, <20 (RG), unknown), reduced urinary output (yes, no (RG), not assessed), vigilance status abnormal due to PE.
Instrumental and laboratory parameters at entry: ECG (with RV overload, without RV overload (RG), not performed), echocardiography (RVD, no RVD (RG), not performed), troponin (increased, not increased (RG), not assessed), BNP/NT-proBNP (increased, not increased (RG), not assessed), hemoglobin (≤10 g/dL, 10–13, >13 (RG), not assessed), creatinine clearance (<30 mL/min, 30–60, >60 (RG), not assessed).
[a]Unknown for 1,472 patients.
[b]Not assessed in 519 patients.
[c]Unknown for 263 patients.
[d]Unknown for 139 patients.
[e]Not performed in 552 patients.
[f]Not performed ≤48 hours in 1,883 patients.
[g]Not performed ≤48 hours in 1,168 patients.
[h]Not performed ≤48 hours in 2,576 patients.
[i]Unknown for 427 patients.
[j]Unknown for 1,105 patients.
Instrumental examinations and laboratory parameters were considered performed at entry only if executed between 24 hours before the EP diagnosis and 48 hours following the EP diagnosis.

deterioration are reported in ►**Supplementary Table S5**, (available in the online version). In particular, decreasing blood pressure, increased respiratory rate, reduced urinary output, active cancer, bed rest for more than 3 days, chronic obstructive pulmonary disease, RVD at echocardiography, and increased troponin were associated with a higher risk of in-hospital death or clinical deterioration.

Discussion

Our contemporary study, the largest registry ever specifically dedicated to patients with acute symptomatic PE, shows that these patients continue to require substantial resource commitment in the acute phase and to have considerable short-term risk of death. Mortality remains elevated in patients classified at high or intermediate risk for death or submassive PE; patients classified at intermediate risk for death also have consistent risk for clinical deterioration during the hospital stay. Almost all patients with acute PE are admitted to the hospital and receive risk stratification assessments and prompt anticoagulation. Direct anticoagulants are the most commonly used anticoagulants after discharge.

A recent review claimed for a progressive decrease in mortality in patients with acute PE over the last 20 years.[5] Overall mortality at 2 weeks from PE diagnosis was 11.4% in late 1990s and 6.7% about 10 years later.[9,10] Our study, with 3.4 and 4.8% in-hospital and 30-day mortalities, seems to confirm a trend toward reduction in mortality. These mortality data could have been impacted by the reduction in the prevalence of patients at high risk for death over time.[9,10] The increased attitude to diagnose less severe PE could have driven this apparent reduction; in fact, 32.6% of patients included in our study were categorized at low risk and 3.4% at high risk for short-term death according to the 2014 ESC model. In the COPE study, in-hospital and 30-day mortalities in patients with high-risk or massive PE overcome 20% while

in patients at intermediate risk or with submassive PE, these were 4% or over. In addition, improved clinical management in terms of rapid diagnosis, prompt anticoagulation, and risk stratification probably contributed to reduce mortality across the whole spectrum of PE patients.

In our study, current strategies for risk stratification effectively identify patients at high and at low risk for death. By means of clinical variable only, the sPESI categorized over one-third of patients as low risk and death at 30 days was as low as 0.5% in these patients; these results confirm the high negative predictive value of the tool, which is confirmed in patients younger than 50 years. Concerning intermediate-risk patients, likewise in a large collaborative European study,[8] we found no additional prognostic value for the combination of RVD and increased troponin compared to either RVD or increased troponin alone in patients with sPESI >0. Additional prognostic value for RVD and increased troponin was shown in previous studies not including sPESI in risk stratification and before the implementation of high-sensitivity troponins.[26] These results renew the concept of need for better strategies for risk stratification of intermediate-risk patients. In this view, reconsidering the role of a large spectrum of clinical risk factor could be of value. Our study shows that some clinical features—reduced urinary output, respiratory rate, etc.—could have a value in risk stratification for the risk of death or clinical deterioration. Moreover, the lack of standardization in the definition of RVD at echocardiography concerning both timing of assessment and parameters could have contributed to drive apparently conflicting results. As an original finding of the COPE study, patients with sPESI >0, no RVD at echocardiography, and normal troponin have a lower risk of death compared to those with sPESI >0 and RVD at echocardiography and/or increased troponin. Whether this specific patient category should be distinct inside the whole group of intermediate-risk patients remains to be defined. Concerning identification of low-risk patients, the combination of sPESI with RVD assessment performed better than either strategy alone. These results are in line with a recent individual patient-data meta-analysis showing an additional predictive value of RVD over sPESI alone[27] and may have a particular value when considering safe selection of candidates for home treatment. The use of both sPESI and right ventricle assessment to identify low-risk patients reduces their proportion from 33 to 17% but improves the accuracy of stratification. This approach leads to an absolute reduction of deaths at 30 days (from 5 to 3 per 1,000) in patients defined at low risk for death, with the counterbalance of a consistent increase in the proportion of intermediate-risk patients that may require hospitalization, and a dilution in their short-term mortality. Identification of patients at very low risk of death can be clinically relevant (although not statistically significant) when the goal is safe discharge from the emergency department. With this strategy, more patients would need to be hospitalized due to "intermediate risk" categorization. However, we observed 0.8% 30-day mortality and 3.8% upgrade to thrombolysis in patients at low risk according to the sPESI but having RVD or increased troponin; these data renew the question on appropriate method for identification of low-risk patients aimed at safely driving clinical management of patients in every-day practice.

Our study describes at least three consistent changes in contemporary clinical management of patients with acute PE. DOACs have become the standard of care. In fact, more than 75% of patients received one of these agents at hospital discharge, and less than 7% received VKAs. These data reveal the confidence of physicians in this "new" treatment approach for an acute potentially fatal cardiovascular disease. Of note, over 90% of patients receive parenteral anticoagulation during the hospital stay.

In terms of diagnosis, almost all patients received CT angiography and only 28% in our study were categorized as at high pretest probability of PE by the attending physician. These data reflect the paradigm change that occurred in the diagnostic process from confirmation of PE in patients at high clinical probability to exclusion of acute PE in patients with low pretest probability of PE.[28–30] The high rate of D-dimer assessment regardless of pretest clinical probability confirms the attitude of physicians to use this test for differential diagnosis of dyspnea or chest pain and may support the advocated changes in the diagnostic pathway.[31] However, the extensive use of D-dimer outside a prespecified diagnostic algorithm can lead to an increase in the use of CT angiography. Finally, we observed an extensive use of risk stratification strategies. The feasibility of right ventricle assessment by echocardiography has spread from cardiology to emergency departments, critical care, and acute care units, due to the improved skill of physicians and to the availability of portable point-of-care echocardiography.[32,33] Moreover, contemporary protocols for the management of patients referred for dyspnea or chest pain include troponin and/or BNP testing.

Overall, our results show that PE still requires a substantial utilization of resources in terms of hospitalization, diagnosis, and risk stratification. Almost all patients in our contemporary study were admitted to short-stay units or regular departments. It is conceivable that implementation of educational strategies and activation of dedicated outpatients' pathways may be crucial to increase clinicians' confidence on home treatment of these patients.[34,35]

We found an association between thrombolytic treatment and death, either in-hospital or at 30 days. As in previous studies,[36] it is conceivable that these results were influenced by the severity of PE in patients receiving thrombolysis. Of importance, a randomized clinical trial is ongoing aimed at better defining the role of thrombolysis in patients with acute PE (NCT04430569).

Our study has some limitations. Mainly, the observation period was intended for 30 days and data on long-term course are not available in the study population. Patients with incidental PE were excluded from the study. Finally, timing of echocardiography or biomarker testing was left to the attending physicians, and sPESI was only calculated at admission. As all these parameters can change during the early phases of admission, this may have influenced their reported prognostic value.

Our study has some strengths. By involving cardiology, internal medicine, and acute care departments and by including critically ill patients dying before consent release, the study has the opportunity to report on the complete spectrum of PE patients. The accrual period of this investigator-initiated study (about 30 months for 5,213 patients in a pandemic era) supports the consecutiveness of study patients and the inclusion of all-comers with PE. The drop-out rate is negligible, and this may reflect the accuracy of follow-up.

In conclusion, acute symptomatic PE continues to be associated with a not negligible risk of death in the short term after diagnosis, which can be predicted by means of risk stratification strategies. Contemporary diagnostic strategies and treatment patterns have substantially changed toward new standards in comparison to previous studies. Further studies are required to refine risk stratification in intermediate-risk patients.

What is known about this topic?

- Acute pulmonary embolism is a common potentially fatal disease.
- The availability of new diagnostic, risk stratification, and treatment strategies makes it crucial to have contemporary data on the management and course of patients with acute PE.

What does this paper add?

- In-hospital mortality and clinical deterioration in patients with high- and intermediate-risk PE continue to be high.
- Diagnostic pathways are partially tailored on pretest clinical probability.
- Acute treatment includes parenteral anticoagulants in almost all patients.
- Direct oral anticoagulants have replaced vitamin K antagonists for the treatment of acute pulmonary embolism.

Authors' Contribution

C.B. and G.A. contributed substantially to study conception and design. C.B., D.L., A.P.M., M.M.G., and G.A. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. D.L. contributed substantially to data analysis. All authors contributed to interpretation of the data, critical revision, and the writing of the manuscript.

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Conflict of Interest

C.B. reports lecture fees and consultancies from Bayer, Bristol Myers Squibb, Pfizer, and Daiichi Sankyo; G.A. reports lecture fees and consultancies from Bayer, Bristol Myers Squibb, and Pfizer; A.P.M., D.L., and M.M.G. declare payments made to their institution from Daiichi Sankyo; F.D. reports lecture fees from Bayer, Bristol Myers Squibb, Pfizer, and Daiichi Sankyo; A.F., I.E., F.P., M.P.R., A.D.L., L.A.C., G.P., and S.C. reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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Daiichi Sankyo had no role on study design, data analysis, and interpretation.

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