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Atrial fibrillation is frequent but does not affect risk stratification in pulmonary embolism

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Abstract. Ebner M, Rogge NIJ, Parwani AS, Sentler C, Lerchbaumer MH, Pieske B, Konstantinides SV, Hasenfuß G, Wachter R, Lankeit M (Charité – University Medicine Berlin; Partner Site, Berlin; University Medical Center, Goettingen; Berlin Institute of Health, Berlin; University Medical Center, Mainz, Germany; Democritus University of Thrace, Alexandroupolis, Greece; Partner Site, Goettingen; University Hospital Leipzig, Leipzig, Germany). Atrial fibrillation is frequent but does not affect risk stratification in pulmonary embolism. *J Intern Med* 2019; https://doi.org/10.1111/joim.12985.

Background. Although prior studies indicate a high prevalence of atrial fibrillation (AF) in patients with pulmonary embolism (PE), the exact prevalence and prognostic impact are unknown.

Methods. We aimed to investigate the prevalence, risk factors and prognostic impact of AF on risk stratification, in-hospital adverse outcomes and mortality in 528 consecutive PE patients enrolled in a single-centre registry between 09/2008 and 09/2017.

Results. Overall, 52 patients (9.8%) had known AF and 57 (10.8%) presented with AF on admission; of those, 34 (59.6%) were newly diagnosed with AF. Compared to patients with no AF, overt hyperthyroidism was associated with newly diagnosed AF (OR 7.89 [2.99–20.86]), whilst cardiovascular risk comorbidities were more frequently observed in patients with known AF. Patients with AF on admission had more comorbidities, presented more frequently with tachycardia and elevated cardiac biomarkers and were hence stratified to higher risk classes. However, AF on admission had no impact on in-hospital adverse outcome (8.3%) and in-hospital mortality (4.5%). In multivariate logistic regression analyses corrected for AF on admission, NT-proBNP and troponin elevation as well as higher risk classes in risk assessment models remained independent predictors of an in-hospital adverse outcome.

Conclusion. Atrial fibrillation is a frequent finding in PE, affecting more than 10% of patients. However, AF was not associated with a higher risk of in-hospital adverse outcomes and did not affect the prognostic performance of risk assessment strategies. Thus, our data support the use of risk stratification tools for patients with acute PE irrespective of the heart rhythm on admission.

Keywords: atrial fibrillation, MR-proANP, prognosis, pulmonary embolism, risk stratification.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting approximately 3% of the adult population [1]. A limited number of cohort studies have demonstrated an association between AF and venous thromboembolism (VTE) that appears to be stronger for pulmonary embolism (PE) than for deep vein thrombosis (DVT) [2, 3]. Patients with known AF are at higher risk for VTE, especially during the first months after AF diagnosis [3, 4]. Conversely, patients with VTE have an increased risk for developing AF during the first 6 months after VTE diagnosis [2].

Atrial fibrillation is an important prognostic factor in many cardiac diseases. The loss of atrial

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contraction as well as high and irregular ventricular rates impair ventricular filling and lead to a reduction in cardiac output by up to 25%, thus potentially worsening haemodynamic instability in acute PE [5, 6]. Although AF is a frequent finding in acute PE affecting 12% to 24% of patients [7–9], the effects of AF on the outcome of PE patients have not been conclusively answered. Studies investigating the influence of AF on the prognosis after PE provided conflicting results regarding in-hospital [7, 10, 11] and 30-day [7, 8] mortality.

Therefore, in the present study we evaluated the prevalence and prognostic impact of AF on in-hospital adverse outcomes and one-year mortality of patients with acute PE. In addition, we investigated whether existing risk stratification tools are affected by the presence of AF and should be adapted considering the heart rhythm at presentation. Furthermore, we compared the characteristics and outcomes of patients with newly diagnosed AF to patients with known AF and patients without AF.

Material and methods

Study design and definition of outcomes

In the present cohort study, patients with objectively confirmed PE ≥ 18 years of age prospectively enrolled in the Pulmonary Embolism Registry of Goettingen (PERGO) at the University Medical Center Goettingen, Germany, between September 2008 and September 2017 were included. The study protocol has been described in detail previously [12, 13]. We excluded patients (i) withdrawing previously given consent for participation in PERGO, (ii) included a second time in PERGO because of recurrent PE, (iii) with missing electrocardiogram (ECG) on admission, (iv) who received cardiopulmonary resuscitation (CPR), electrical cardioversion or suffered from a sustained ventricular arrhythmia before admission and (v) with subsegmental PE in combination with significant acute cardiorespiratory illness responsible for clinical presentation and symptoms (Fig. 1). All patients were followed for the in-hospital stay,

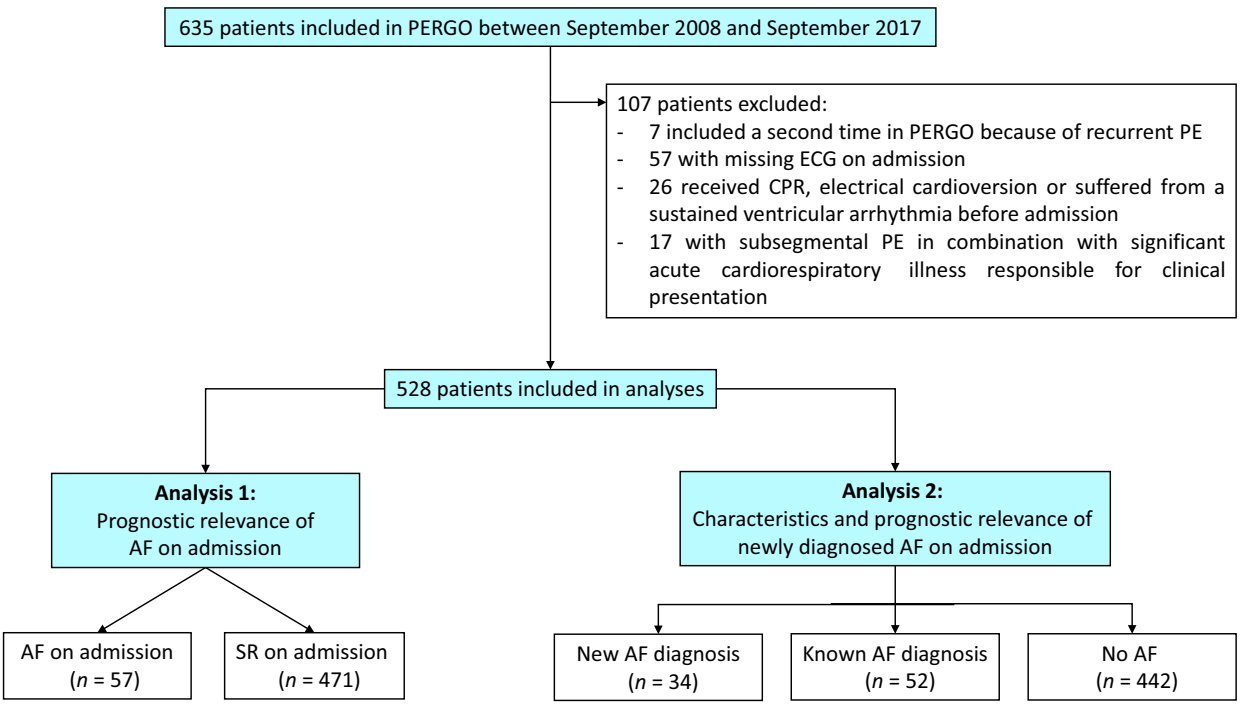

Fig. 1 *Flowchart of study design. Patients included in the analysis were stratified (a) according to the heart rhythm on admission and (b) based on whether AF was known or not. AF, atrial fibrillation; CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; PE, pulmonary embolism; PERGO denotes Pulmonary Embolism Registry of Goettingen; SR, sinus rhythm.*

and one-year survival status was assessed by contacting the responsible registration offices.

The diagnostic and therapeutic management was in accordance with the ESC 2008 (09/2008–08/2014) and 2014 (09/2014–09/2017) guidelines [14, 15] and local standard operating procedures. All related decisions were left to the discretion of the treating physicians and were not influenced by the study protocol. Treating physicians were not informed about study results, and thus, any influence of the study on patient management or monitoring of treatment effects can be excluded. The study was conducted in accordance with the amended Declaration of Helsinki and was approved by the local independent Ethic Committee of the Medical University Goettingen, Germany; all patients gave informed written consent for participation in the study.

Complete data on baseline characteristics, VTE risk factors and comorbidities, results from diagnostic examinations including imaging (computed tomography pulmonary angiography [CTPA] and transthoracic echocardiography [TTE]) and laboratory testing, treatment and in-hospital outcomes were obtained using a standardized case report form. Heart rhythm was assessed from admission ECGs and independently adjudicated by two blinded authors (N.I.J.R. and M.L.), and disagreement was resolved by a third author (A.S.P.). RV dysfunction on CTPA was defined as right-to-left (RV/LV) diameter ratio $\geq$ 1.0. RV dysfunction on TTE was defined as RV dilatation (end-diastolic diameter >30 mm from the parasternal view or a RV/LV diameter ratio $\geq$ 1.0 from the subcostal or apical view) combined with right atrial hypertension (the absence of inspiratory collapse of the inferior vena cava) [16]. Active cancer was defined as known disease, treatment with antitumor therapy within the last 6 months, metastatic state or haematologic cancer that was not in complete remission [17].

Individual risk stratification was performed according to the algorithm proposed by the ESC 2014 guidelines [15], the simplified Pulmonary Embolism Severity Index (sPESI) and the modified FAST score [18]. For calculation of algorithms and scores, missing values were considered to be normal [18].

As shown in Fig. 1, study patients were stratified (i) according to the heart rhythm on admission (AF vs. sinus rhythms) and (ii) based on whether AF was known or newly diagnosed on admission.

An in-hospital adverse outcome was defined as PE-related death, cardiopulmonary resuscitation or administration of catecholamines. Further study outcomes include in-hospital all-cause death, duration of the in-hospital stay (days) and one-year all-cause mortality. Death was determined to be PE-related if either confirmed by autopsy or following a clinically severe episode of acute PE in the absence of an alternative diagnosis. All events and causes of death were independently adjudicated by two of the authors (M.E. and N.I.J.R.), and disagreement was resolved by a third author (M.L.).

Biomarker measurements

Venous blood samples were collected on admission, processed using standard operating procedures and immediately stored at −80 °C. Plasma concentrations of mid-regional pro-atrial natriuretic peptide (MR-proANP; BRAHMS GmbH, Thermo Fisher Scientific, Hennigsdorf/Berlin, Germany), high-sensitivity troponin T (hsTnT; Roche Diagnostics, Mannheim, Germany) and N-terminal pro-brain natriuretic peptide (NT-proBNP; Roche Diagnostics, Mannheim, Germany) were measured in batches after a single thaw by amedes MVZ wagnerstibbe, Goettingen, Germany. Elevated biomarker concentrations were prospectively defined as hsTnT $\geq$ 14 pg mL^{-1} [19], NT-pro BNP $\geq$ 600 pg mL^{-1} [20] and MR-proANP $\geq$ 120 pmol L^{-1} [21].

Statistical analysis

Categorical variables are presented as total numbers and percentages; continuous variables not following a normal distribution if tested with Kolmogorov–Smirnov test are presented as medians with interquartile ranges (IQR). Associations between binary and categorical variables were analysed using Fisher's exact test or chi-squared test, as appropriate. For comparison of continuous variables, the Mann–Whitney *U*-test was employed.

To allow comparison of scores, the four-level ESC 2014 algorithm was dichotomized as low risk and intermediate–low risk ('low risk') versus intermediate–high risk and high risk ('high risk') [18]. The prognostic relevance of AF, patient characteristics and comorbidities, biomarkers and risk assessment strategies/scores with regard to study outcomes was tested using univariable logistic regression analyses, and results are presented as odds ratios (OR) with the corresponding 95% confidence intervals (CIs). To investigate the

prognostic role of different risk stratification markers in the presence of AF, we conducted multivariate logistic regression analyses. Kaplan–Meier analysis was used to compare the probability of one-year survival in subgroups stratified (i) according to heart rhythm on admission and (ii) based on whether AF was known or not; the log-rank test was used for comparison. Cox regression analysis was used to identify predictors of one-year survival in patients discharged from hospital alive; results are presented as hazard ratios (HR) with the corresponding 95% CIs.

A two-sided significance level of $\alpha < 0.05$ was defined as appropriate to indicate statistical significance. As this was an explorative testing, no adjustments for multiple testing were carried out. *P*-values were provided for descriptive reasons only and should be interpreted with caution and in connection with effect estimates. Statistical analysis was performed using Statistics Package for Social Sciences (IBM SPSS Statistics, version 25, IBM Corp. Armonk, NY).

Results

Of 635 patients enrolled in PERGO between September 2008 and September 2017, 107 patients (16.9%) were excluded from analysis (Fig. 1). Information on baseline characteristics and risk stratification of the 528 study patients are presented in Table 1, left column. On admission, 57 patients (10.8%) presented with AF; of those, 34 (59.6%) had a first documented AF episode. Of 52 patients (9.8%) with known AF, 23 (44.2%) patients presented with AF on admission (Fig. 1).

As shown in Table 1, right columns, patients presenting with AF were older and more frequently had chronic heart failure, coronary artery disease, renal insufficiency and overt hyperthyroidism compared with patients presenting in SR (Table 1, right columns). In addition, AF patients more frequently presented with tachycardia, elevated cardiac biomarkers and were hence more often stratified to higher risk classes by the ESC 2014 algorithm, sPESI and modified FAST score.

Prognostic impact of AF on admission

Overall, 44 patients (8.3%) had an in-hospital adverse outcome and 24 patients (4.5%) died during the in-hospital stay, of those 13 (54.2%) due to PE. Interestingly, AF on admission was neither associated with an increased risk of an in-hospital adverse outcome nor in-hospital all-cause mortality (Table 2A). In the subgroup of 501 normotensive patients, a higher rate of an adverse outcome was observed in patients with AF on admission compared with patients presenting in SR (9.6% vs. 5.1%); however, this finding did not reach statistical significance (OR 1.93 [95% CI 0.54–6.89]; Table 2B). Further, AF was not associated with adverse outcomes focussing on other subgroups of interest (women, patients with chronic heart failure, RV dysfunction on TTE/CTPA or intermediate–high risk/high risk according to risk stratification algorithms/scores; data not shown). However, patients presenting with AF on admission had a longer median duration of in-hospital stay compared with patients presenting in SR (Table 1).

Of 504 patients discharged from hospital alive, information on the survival status at one year was available for 496 patients (98.4%). During the first year after PE, 53 patients (10.7%) died after hospital discharge. AF on admission was not associated with an increased risk (Table S1 of the supplementary material) or probability of one-year mortality (Figure S1 of the supplementary material).

Relevance of AF on admission for the prognostic performance of risk assessment strategies

As shown in Table 3A, left column, elevated levels of hsTnT, NT-proBNP and MR-proANP, tachycardia and classification to higher risk classes according to the sPESI, modified FAST score and ESC 2014 algorithm were identified as predictors of an in-hospital adverse outcome. Importantly, adjustment for AF on admission using multivariate models did not affect their prognostic performance (Table 3A, right column). Although AF on admission was not predictive of in-hospital adverse outcome or death, AF was associated with elevated cardiac biomarkers, tachycardia and higher risk classes in algorithms and scores (Table S2 of the supplementary material). The strongest effect of AF on admission was observed on MR-proANP ≥ 120 pmol L^{-1} (OR 45.3 [95% CI 6.2–331.0]). Furthermore, risk assessment models were able to predict in-hospital mortality, whilst single parameters such as tachycardia or cardiac biomarkers were not of predictive value in our cohort (Table 3B). Similar results were obtained focussing on normotensive patients only (Table S3 of the supplementary material).

Table 1. *Characteristics of PE patients presenting with and without AF on admission*

	All patients (n = 528)	AF on admission (n = 57)	SR on admission (n = 471)	P-value
Age (years)	70 (55–78)	76 (73–83)	68 (54–77)	**<0.001**
Sex (female)	281 (53.2%)	34 (59.6%)	247 (52.4%)	0.33
BMI (kg m^{-2})	27.7 (24.4–31.1), n = 509	27.7 (22.8–32.6), n = 53	27.7 (24.5–27.7), n = 456	0.88
Comorbidities				
Chronic heart failure	84 (15.9%)	16 (28.1%)	68 (14.4%)	**0.012**
Coronary artery disease	96 (18.2%)	19 (33.3%)	77 (16.3%)	**0.003**
Chronic pulmonary disease	81 (15.3%)	10 (17.5%)	71 (15.1%)	0.70
Arterial hypertension	336 (63.6%)	42 (73.7%)	294 (62.4%)	0.11
Diabetes mellitus	93 (17.6%)	14 (24.6%)	79 (16.8%)	0.14
Renal insufficiency (GFR < 60 mL min^{-1}/1.73 m^2)	181 (34.7%), n = 522	29 (51.8%)	152 (32.6%), n = 466	**0.007**
Active cancer	76 (14.4%)	7 (12.3%)	69 (14.6%)	0.84
Overt hyperthyroidism	23 (4.4%), n = 518	8 (14.3%), n = 56	15 (3.2%), n = 462	**<0.001**
Prior medication				
Betablocker	222 (42.7%), n = 520	37 (64.9%)	185 (40.0%), n = 463	**<0.001**
Other antiarrhythmic drugs	15 (2.9%), n = 520	4 (7.0%)	11 (2.4%), n = 463	**0.048**
Therapeutic anticoagulation	28 (5.3%)	8 (14.0%)	20 (4.2%)	**0.006**
Prophylactic anticoagulation	45 (8.5%)	4 (7.0%)	41 (8.7%)	0.81
Antiplatelet agents	166 (31.4%), n = 527	28 (49.1%)	138 (29.4%), n = 470	**0.002**
Vital signs				
Heart rate (/min)	90 (76–105), n = 519	105 (89–130), n = 56	88 (75–104), n = 463	**<0.001**
Tachycardia (heart rate ≥ 100/min)	187 (36.0%), n = 519	34 (60.7%), n = 56	153 (33.0%), n = 463	**<0.001**
Systolic blood pressure (mmHg)	130 (119–150), n = 511	128 (107–140), n = 55	130 (120–150), n = 456	0.19
Hypotension (systolic blood pressure < 90 mmHg)	24 (4.7%), n = 511	3 (5.5%), n = 55	21 (4.6%), n = 456	0.78
Hypoxaemia (SpO_2 < 90 %)	122 (27.2%), n = 448	12 (24%), n = 50	110 (27.6%), n = 398	0.74
Signs of RV dysfunction and atrial dilatation				
RV dysfunction on TTE/CTPA	401 (75.9%)	44 (77.2%)	357 (75.8%)	0.87
RV dysfunction on TTE	148 (47.6%), n = 311	15 (44.1%), n = 34	133 (48.0%), n = 277	0.72

Table 1 (*Continued*)

	All patients (n = 528)	AF on admission (n = 57)	SR on admission (n = 471)	P-value
RV/LV diameter ratio ≥ 1.0 on CTPA	373 (81.4%), n = 458	41 (85.4%), n = 48	332 (81.0%), n = 410	0.56
LA volume on CTPA (mL)	728 (57–94), n = 458	106 (77–139), n = 48	70 (56–90), n = 410	**<0.001**
RA volume on CTPA (mL)	105 (81–137), n = 458	139 (114–178), n = 48	101 (79–132), n = 410	**<0.001**
Cardiac biomarkers				
hsTnT ≥ 14 pg mL^{-1}	314 (67.0%), n = 469	41 (80.4%), n = 51	273 (65.3%), n = 418	**0.039**
NT-proBNP ≥ 600 pg mL^{-1}	263 (55.3%), n = 476	46 (90.2%), n = 51	217 (51.1%), n = 425	**<0.001**
MR-proANP ≥ 120 pmol L^{-1}	245 (55.3%), n = 443	47 (97.9%), n = 48	198 (50.1%), n = 395	**<0.001**
Risk stratification				
ESC 2014 algorithm				
Low risk	85 (16.1%)	2 (3.5%)	83 (17.6%)	**0.002**
Intermediate–low risk	201 (38.1%)	16 (28.1%)	185 (39.3%)	
Intermediate–high risk	215 (40.7%)	35 (61.4%)	180 (38.2%)	
High risk	27 (5.1%)	4 (7.0%)	23 (4.9%)	
sPESI ≥ 1 point	357 (67.6%)	51 (89.5%)	306 (65.0%)	**<0.001**
Modified FAST score ≥ 3 points	160 (30.3%)	28 (49.1%)	132 (28.0%)	**0.002**
Outcomes				
Duration of in-hospital stay (days)	9 (5–14)	10 (7–19)	9 (5–13)	**0.021**
In-hospital adverse outcome	44 (8.3%)	5 (8.8%)	39 (8.3%)	0.80
In-hospital all-cause mortality	24 (4.5%)	2 (3.5%)	22 (4.7%)	1.00
One-year mortality	77 (14.8%), n = 520	10 (17.5%), n = 57	67 (14.5%), n = 463	0.54

If data were not available for all patients, n refers to the number of patients with available data. P-values < 0.05 are marked in bold.
AF, denotes atrial fibrillation; BMI, body mass index; CTPA, computed tomography pulmonary angiography; ESC, European society of cardiology; GFR, glomerular filtration rate; hsTnT, high-sensitivity troponin T; LV, left ventricle; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; RV, right ventricle; sPESI, simplified pulmonary embolism severity index; SpO2, peripheral oxygen saturation; SR, sinus rhythm; TTE, transthoracic echocardiography.

Prevalence and prognostic relevance of newly diagnosed AF on admission

To assess the prognostic importance of a newly diagnosed AF at the time of admission for acute PE, we compared baseline characteristics, initial risk stratification and outcome of patients with a newly diagnosed AF to patients with known AF and patients without AF. Whilst relevant cardiovascular comorbidities were more often present in

Table 2. *Prognostic impact of AF on admission*

	SR on admission (n = 471)	AF on admission (n = 57)	Unadjusted OR (95% CI)	P-value	Newly diagnosed AF on admission (n = 34)	Unadjusted OR (95% CI)	P-value
A: All patients (n = 528)							
In-hospital adverse outcome	39 (8.3%)	5 (8.8%)	1.06 (0.40–2.82)	0.89	3 (8.8%)	1.07 (0.31–3.67)	0.91
In-hospital all-cause mortality	22 (4.7%)	2 (3.5%)	0.74 (0.17–3.24)	0.69	0 (0.0%)	n.c.[a]	1.00
One-year mortality	67 (14.5%), n = 463	10 (17.5%)	1.26 (0.61–2.61)	0.55	4 (11.8%)	0.79 (0.27–2.31)	0.80
	SR on admission (n = 448)	AF on admission (n = 52)	Unadjusted OR (95% CI)	P-value	Newly diagnosed AF on admission (n = 31)	Unadjusted OR (95% CI)	P-value
B: Normotensive patients (n = 501)							
In-hospital adverse outcome	23 (5.1%)	5 (9.6%)	1.93 (0.70–5.30)	0.21	3 (9.7%)	1.98 (0.56–7.00)	0.29
In-hospital all-cause mortality	17 (3.8%)	2 (3.8%)	0.99 (0.22–4.43)	0.99	0 (0.0%)	n.c.[a]	1.00
One-year mortality	56 (12.7%), n = 440	8 (15.1%), n = 53	1.25 (0.56–2.79)	0.59	3 (9.4%)	0.74 (0.22–2.50)	0.78

If data were not available for all patients, n refers to the number of patients with available data.
AF, denotes atrial fibrillation; CI, confidence interval; OR, odds ratio; SR, sinus rhythm.
[a]Could not be calculated due to a sensitivity of 1.00.

Table 3. *Prognostic value of biomarkers and risk assessment strategies*

	Univariate model		Multivariate model (adjusted for AF on admission)	
	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
A: In-hospital adverse outcome				
hsTnT ≥ 14 pg mL^{-1}	9.29 (2.20–39.19)	**0.002**	9.22 (2.18–38.95)	**0.003**
NT-proBNP ≥ 600 pg mL^{-1}	6.39 (2.46–16.61)	**<0.001**	6.88 (2.63–18.02)	**<0.001**
MR-proANP ≥ 120 pmol L^{-1}	7.71 (2.70–22.05)	**<0.001**	8.57 (2.97–24.70)	**<0.001**
RV/LV diameter ratio ≥ 1.0 on CTPA	1.45 (0.55–3.84)	0.46	1.44 (0.54–3.81)	0.47
Tachycardia (heart rate ≥ 100/min)	2.08 (1.09–3.99)	**0.026**	2.09 (1.08–4.04)	**0.028**
ESC 2014 algorithm: intermediate–high/high risk vs. intermediate–low/low risk	10.80 (4.18–27.87)	**<0.001**	11.17 (4.31–28.95)	**<0.001**
sPESI ≥ 1 point(s)	11.27 (2.69–47.12)	**0.001**	11.55 (2.75–48.45)	**0.001**
Modified FAST score ≥ 3 points	2.77 (1.48–5.18)	**0.001**	2.82 (1.50–5.29)	**0.001**
B: In-hospital mortality				
hsTnT ≥ 14 pg mL^{-1}	3.26 (0.95–11.20)	0.06	3.33 (0.97–11.46)	0.06
NT-proBNP ≥ 600 pg mL^{-1}	1.94 (0.73–5.14)	0.18	2.17 (0.81–5.81)	0.12
MR-proANP ≥ 120 pmol L^{-1}	2.52 (0.90–7.05)	0.08	2.93 (1.03–8.29)	**0.043**
RV/LV diameter ratio ≥ 1.0 on CTPA	2.08 (0.91–4.77)	0.08	2.09 (0.91–4.80)	0.08
Tachycardia (heart rate ≥ 100/min)	1.82 (0.78–4.29)	0.17	1.89 (0.80–4.51)	0.15
ESC 2014 algorithm: intermediate–high/high risk vs. intermediate–low/low risk	3.75 (1.46–9.61)	**0.006**	3.94 (1.53–10.14)	**0.005**
sPESI ≥ 1 point(s)	11.71 (1.57–87.42)	**0.016**	12.34 (1.65–92.40)	**0.014**
Modified FAST score ≥ 3 points	2.41 (1.06–5.48)	**0.037**	2.51 (1.09–5.75)	**0.030**

P-values < 0.05 are marked in bold.
CI, confidence interval; CTPA, computed tomography pulmonary angiography; ESC, European society of cardiology; hsTnT, high-sensitivity troponin T; LV, left ventricle; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; OR denotes odds ratio; RV, right ventricle; sPESI, simplified pulmonary embolism severity index.

patients with known AF, the prevalence of these comorbidities did not differ between patients with a newly diagnosed AF and patients without AF (Table 4). On the other hand, overt hyperthyroidism was associated with newly diagnosed AF on admission (OR 7.89 [2.99–20.86]).

As shown in Table 4, newly diagnosed AF, but not known AF, was associated with tachycardia on admission. Of note, a higher median heart rate was observed in patients with known AF presenting with AF compared with those with SR on admission (98 [IQR 86–120]/min versus 75 [IQR 64–94]/min; $P = 0.016$). Both subgroups of AF patients were treated to a similar proportion with beta blockers and other antiarrhythmic drugs (Table 4).

Interestingly, although 48 of 52 (93.4%) patients with known AF had a CHA_2DS_2-VASc score ≥ 2 points, only 12 (23.1%) patients received therapeutic anticoagulation on admission. Additionally, three of nine patients (33.3%) treated with vitamin-K antagonists had an international normalized ratio (INR) <2.0, so only 9 of 52 (17.3%) patients with known AF were adequately treated.

Discussion

In the present real-world single-centre cohort investigating 528 PE patients included consecutively over a 9-year period, 10.8% of patients presented with AF on admission; of those, 59.6% had newly diagnosed AF. The prevalence of known

Table 4. *Comparison of comorbidities, findings on admission and outcomes of PE patients with newly diagnosed AF, known AF and no AF on admission*

	Newly diagnosed AF (n = 34)	P-value[a]	No AF (n = 442)	P-value[b]	Known AF (n = 52)
Age (years)	74 (67–80)	**0.002**	68 (53–76)	**<0.001**	77 (70–84)
Sex (female)	21 (61.8%)	0.38	237 (53.6%)	0.24	23 (44.2%)
BMI (kg m^{-2})	27.8 (24.9–32.7), n = 31	0.99	27.7 (24.3–31.1), n = 427	0.88	27.7 (24.7–31.3), n = 51
Comorbidities					
Chronic heart failure	7 (20.6%)	0.22	58 (13.1%)	**<0.001**	19 (36.5%)
Coronary artery disease	9 (26.5%)	0.09	66 (14.9%)	**<0.001**	21 (40.4%)
Chronic pulmonary disease	4 (11.8%)	0.69	63 (14.3%)	**0.025**	14 (26.9%)
Arterial hypertension	26 (76.5%)	0.07	268 (60.6%)	**0.004**	42 (80.8%)
Diabetes mellitus	8 (23.5%)	0.22	68 (15.4%)	**0.003**	17 (32.7%)
Renal insufficiency (GFR < 60 mL min^{-1}/1.73 m^2)	14 (42.4%), n = 33	0.25	137 (31.3%), n = 438	**<0.001**	30 (58.8%), n = 51
Active cancer	3 (8.8%)	0.35	65 (14.7%)	0.84	8 (15.4%)
Overt hyperthyroidism	7 (21.2%), n = 33	**<0.001**	14 (3.2%), n = 433	0.82	2 (3.8%)
Prior medication					
Beta blocker	22 (64.7%)	**0.003**	164 (37.8%), n = 434	**<0.001**	36 (69.2%)
Other antiarrhythmic drugs	3 (8.8%)	**0.005**	7 (5.2%), n = 434	**<0.001**	5 (9.6%)
Therapeutic anticoagulation	1 (3.2%)	1.00	15 (3.4%)	**<0.001**	12 (23.1%)
Prophylactic anticoagulation	3 (8.8%)	1.00	38 (8.6%)	1.00	4 (7.7%)
Antiplatelet agents	15 (44.1%)	**0.032**	119 (26.9%), n = 441	**<0.001**	32 (61.5%)
Vital signs on admission					
Heart rate (/min)	118 (87–134), n = 34	**<0.001**	88 (76–104), n = 435	0.46	87 (70–105), n = 50
Tachycardia (heart rate ≥ 100/min)	23 (67.6%)	**<0.001**	148 (34.0%), n = 435	0.88	16 (32.0%), n = 50
Systolic blood pressure (mmHg)	125 (104–140), n = 33	0.18	130 (120–150), n = 429	0.30	130 (110–140), n = 49
Hypotension (systolic blood pressure < 90 mmHg)	1 (3.0%), n = 33	0.70	19 (4.4%), n = 429	0.25	4 (8.2%), n = 49
Hypoxaemia (SpO2 < 90 %)	7 (22.6%), n = 31	0.68	104 (27.6%), n = 377	0.99	11 (27.5%), n = 40
Signs of RV dysfunction and atrial dilatation					
RV dysfunction on TTE/CTPA	24 (70.6%)	0.54	334 (75.6%)	0.30	43 (82.7%)
RV dysfunction on TTE	9 (42.9%), n = 21	0.82	125 (47.5%), n = 263	0.69	14 (51.9%), n = 27
RV/LV diameter ratio ≥ 1.0 CTPA	22 (81.5%), n = 27	1.00	312 (80.4%), n = 388	0.15	39 (90.7%), n = 43
LA volume on CTPA (mL)	93 (67–114), n = 27	**<0.001**	70 (55–88), n = 388	**<0.001**	103 (80–140), n = 43
RA volume on CTPA (mL)	128 (109–167), n = 27	**<0.001**	100 (79–130), n = 388	**<0.001**	135 (106–178), n = 43
Cardiac biomarkers					

Table 4 (*Continued*)

	Newly diagnosed AF (n = 34)	P-value[a]	No AF (n = 442)	P-value[b]	Known AF (n = 52)
hsTnT ≥ 14 pg mL^{-1}	22 (75.9%), n = 29	0.23	253 (64.4%), n = 393	**0.013**	39 (83.0%), n = 47
NT-proBNP ≥ 600 pg mL^{-1}	27 (87.1%), n = 31	**<0.001**	199 (49.6%), n = 401	**<0.001**	7 (84.1%), n = 44
MR-proANP ≥ 120 pmol L^{-1}	27 (96.4%), n = 28	**<0.001**	180 (48.3%), n = 373	**<0.001**	38 (90.5%), n = 42
Risk stratification					
ESC 2014 algorithm:					
Low risk	2 (5.9%)	0.14	80 (18.1%)	**0.002**	3 (5.8%)
Intermediate–low risk	12 (35.2%)		174 (39.4%)		15 (28.8%)
Intermediate–high risk	18 (52.9%)		168 (38%)		29 (55.8%)
High risk	2 (5.9%)		20 (4.5%)		5 (9.6%)
sPESI ≥ 1 point(s)	29 (85.3%)	**0.014**	285 (64.5%)	**0.008**	43 (82.7%)
Modified FAST score ≥ 3 points	20 (58.8%)	**<0.001**	126 (28.5%)	0.872	14 (26.9%)
Outcomes					
Duration of in-hospital stay (days)	12 (7–19)	**0.018**	9 (5–13)	0.05	11 (6–16)
In-hospital adverse outcome	3 (8.8%)	0.75	36 (8.1%)	0.72	5 (9.6%)
In-hospital all-cause mortality	0 (0%)	0.21	20 (4.5%)	0.33	4 (7.7%)
One-year mortality	4 (11.8%)	0.70	62 (14.2%), n = 437	0.14	11 (22.4%), n = 49

P-values < 0.05 are marked in bold.
If data were not available for all patients, n refers to the number of patients with available data.
AF, denotes atrial fibrillation; BMI, body mass index; CTPA, computed tomography pulmonary angiography; ESC, European society of cardiology; GFR, glomerular filtration rate; hsTnT, high-sensitivity troponin T; LA, Left atrium; LV, left ventricle; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; RA, right atrium; RV, right ventricle; sPESI, simplified pulmonary embolism severity index; SpO2, peripheral oxygen saturation; TTE, transthoracic echocardiography.
[a]Patients with newly diagnosed AF (left column) were compared with patients with no AF (middle column).
[b]Patients with known AF (right column) were compared with patients with no AF (middle column).

or newly diagnosed AF of 16.3% in the present study was higher compared with the German population (4.7% and 7.6% for patients aged 65–69 and 70–74 years, respectively) [22]. Patients with AF on admission had more comorbidities, presented more frequently with tachycardia and elevated cardiac biomarkers and were hence stratified to higher risk classes. Importantly, AF on admission had no impact on in-hospital adverse outcomes and did not affect the prognostic performance of biomarkers and risk assessment strategies. Baseline characteristics of patients with newly diagnosed AF and patients with known AF differed. Whilst cardiovascular comorbidities were more frequent in patients with known AF, patients with newly diagnosed AF had more often overt hyperthyroidism.

Prognostic impact of AF on admission

The few previous reports that investigated the prognostic relevance of AF on admission for acute PE provided contradicting results. An analysis of 508 PE patients derived from a prospective registry published in 2005 reports that nonsurvivors more frequently had atrial arrhythmias on admission compared with survivors (25% vs. 12%, $P < 0.001$) [8]. However, since this registry only included patients with 'major PE' (defined as haemodynamic instability or RV dysfunction or signs of pulmonary hypertension on TTE or right heart catheterization), results are not generalizable. Koracevic et al. conducted a smaller study with 140 PE patients and found no impact of AF on in-hospital mortality, similar to the findings of our study [11]. However, important methodological and outcome information are missing and limit interpretability of these findings. An analysis by Krajewska et al. investigating the effect of AF during hospitalization for acute PE (rather than on admission) in 391 patients reported that paroxysmal AF had little effect on all-cause mortality compared with sinus rhythm (mortality rate 6.5% and 5.0%, respectively), but observed a higher in-hospital mortality rates in patients with permanent AF (25%) [10]. The remarkable high mortality rate in the latter group might be partially explained by an uneven distribution of other relevant prognostic factors, such as a lower median LV ejection fraction and renal function in the permanent AF group. Hence, the observed differences in mortality might not be exclusively due to the effects of atrial fibrillation. Our study considerably adds to these previous investigations. We report on the yet largest population of well characterized and consecutive PE patients. In contrast to Krajewska et al., we did not investigate the effects of different AF types occurring over the course of hospitalization, but focused on the heart rhythm on admission, the critical time-point for risk assessment and therapeutic decision-making.

In contrast to our study hypothesis, AF on admission was no predictor of an in-hospital adverse outcome and mortality. Nevertheless, two findings might hint towards a prognostic impact of AF in acute PE: First, normotensive patients with AF on admission had a numerically higher rate of an adverse outcome compared with patients presenting in SR (9.6% vs. 5.1%). Secondly, AF was associated with tachycardia and elevated cardiac biomarkers; thus, patients with AF on admission were stratified to higher risk classes by the ESC 2014 algorithm, the sPESI and the modified FAST score. Therefore, the prognostic impact of AF in acute PE more likely appears to be small rather than absent and a larger sample size would have been required to demonstrate statistical differences. However, as patients with known AF receive therapeutic anticoagulation for prevention of stroke and are thus protected from developing acute PE, inclusion of a large number of patients with PE and AF is challenging.

MR-proANP, secreted from the atria as a result of increased wall tension and stretch [23], was strongly associated with the presence of AF in our PE patients. MR-proANP levels ≥ 120 pmol L^{-1} were found in 97.9% of patients with AF on admission compared with 50.1% in patients presenting in SR. Despite this fact, elevation of MR-proANP (as well as elevated hsTnT and NT-proBNP levels) was associated with an increased risk of an in-hospital adverse outcome regardless of the presence of AF (Table 3A) indicating the MR-proANP integrates different prognostic relevant information from comorbidities.

Importantly, we are the first to demonstrate that the prognostic performances of established risk assessment strategies and biomarkers are not affected by the presence of AF. This finding supports the use of risk stratification for patients with acute PE irrespective of heart rhythm on admission.

Differences of PE patients with newly diagnosed AF and known AF

The incidence, risk factors and prognostic implications of newly diagnosed AF on admission for acute

PE have not been investigated so far. In our cohort, as many as 59.6% of PE patients presenting with AF on admission had no history of AF. These patients with newly diagnosed AF differ from patients with known AF in several important aspects: Not surprisingly, patients with known AF had a higher prevalence of chronic heart failure, coronary artery disease, chronic pulmonary disease, arterial hypertension, diabetes mellitus and renal insufficiency compared with patients without AF. In contrast, the prevalence of these comorbidities was lower in PE patients with newly diagnosed AF. However, patients with newly diagnosed AF more often had overt hyperthyroidism, a condition known for its pro-arrhythmogenic potential [1]. Further studies are needed to investigate to which extent PE might trigger AF or whether patients with newly diagnosed AF actually suffered from undiagnosed paroxysmal AF prior to PE. Further, the implications of newly diagnosed AF on the optimal duration of long-term anticoagulation remain unclear. Thus, studies that explore the long-term risk of ischaemic stroke after discontinuation of anticoagulation in patients with newly diagnosed AF at presentation for acute PE are warranted.

Of note, 9.8% our PE patients had known AF. Although all but four of these patients had a CHA_2DS_2-VASc score ≥ 2 points and therefore should have been treated with therapeutic anticoagulation for prevention of arterial thromboembolism [1], only 23.1% of patients with known AF received therapeutic anticoagulation at the time of PE diagnosis. However, the large proportion of nonanticoagulated AF patients in our cohort most likely reflects the effective prevention of VTE in AF patients who receive guideline-recommended anticoagulation treatment.

Conclusion

Atrial fibrillation is a frequent finding in patients with acute PE, present in more than 10% of cases. Of those, more than 50% had no previous AF diagnosis. These newly diagnosed AF patients had a distinct pattern of risk factors compared with patients without AF or patients with known AF. Although not predictive of in-hospital adverse outcomes in our cohort, patients with AF on admission were more frequently classified to higher risk classes due to tachycardia and elevated cardiac biomarker levels. Importantly, the prognostic performance of risk assessment strategies was not affected by AF. Thus, our data support the use of risk stratification tools for patients with acute PE irrespective of the heart rhythm on admission.

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Conflict of interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Probability of one-year all-cause mortality in PE patients discharged alive from hospital.

Table S1. Predictors of one-year mortality in 496 patients discharged alive from hospital.

Table S2. Odds of AF on admission for having elevated biomarkers, RV dysfunction or higher risk scores in PE patients.

Table S3. Prognostic value of biomarkers and risk assessment strategies in normotensive patients.

