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Full Length Article

# Evolving patterns of intracranial hemorrhage in advanced therapies in patients with acute pulmonary embolism

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ABSTRACT

*Background:* Dissecting trends and contributing risk factors for intracranial hemorrhage (ICH) in patients treated for acute pulmonary embolism (PE) may allow for a better patient selection for existing and emerging treatment options.

*Methods:* The German nationwide inpatient sample was screened for patients admitted due to PE 2005–2020. Hospitalizations were stratified for the occurrence of ICH; risk factors for ICH and temporal trends were investigated.

*Results:* Overall, 816,653 hospitalizations due to acute PE in the period 2005–2020 were analyzed in the study. ICH was reported in 2516 (0.3 %) hospitalizations, and time trend analysis revealed a fluctuating but overall, largely unchanged annual incidence. There was an increase of ICH with age. Patients with ICH had a higher comorbidity burden (Charlson-Comorbidity-Index [CCI], 5.0 [4.0–7.0] vs. 4.0 [2.0–5.0]; $P < 0.001$), and higher CCI was associated with an OR of 1.26 (95%CI 1.24–1.27) for ICH. Further independent risk factors for ICH were age $\geq$ 70 years (OR 1.23 [1.12–1.34]), severe (versus low-risk) PE (OR 3.09 [2.84–3.35]), surgery (OR 1.59 [1.47–1.72]), acute kidney injury (OR 3.60 [3.09–4.18]), and ischemic stroke (OR 14.64 [12.61–17.00]). The identified risk factors for ICH varied among different reperfusion treatment groups. As expected, ICH had a substantial impact on case-fatality of PE (OR 6.16 [5.64–6.72]; $P < 0.001$).

*Conclusions:* Incidence of ICH in patients hospitalized for acute PE in Germany was overall low and depended on the patients' comorbidity burden. Identifying patients at risk for ICH allows tailored patient selection for the different reperfusion treatments and might prevent ICH.

## 1. Introduction

Pulmonary embolism (PE), is the third most common acute cardiovascular disease affecting 39–115 individuals per 100,000 population [1,2]. It is a potentially life-threatening condition variating widely in its clinical manifestation, ranging from asymptomatic to cardiorespiratory decompensation and sudden cardiac death [3]. Recent data from Europe and the United States (US) suggest that its incidence and hospitalization

*Abbreviations:* PE, pulmonary embolism; US, United States; VTE, venous thromboembolism; CDT, catheter-directed treatment; ICH, intracranial hemorrhage; RDC, research data center; IQR, interquartile range; CI, confidence interval; CCI, Charlson Comorbidity Index; VTE-BLEED, Venous Thromboembolic Disease & Bleeding; ERICH, Ethnic/Racial Variations of Intracerebral Hemorrhage; AF, atrial fibrillation/flutter.

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rates are constantly rising while case-fatality decreases [2,4].

To resolve emboli and prevent recurrence of venous thromboembolism (VTE), anticoagulation treatment is a key component of PE therapy [1]. However, in approximately 30 % of all PE events, which are classified as intermediate-high or high-risk based on impending or overt clinical and hemodynamic decompensation, anticoagulant treatment alone is often not sufficient to reduce the risk of early death [1]. Therefore, early use of reperfusion treatment, primarily systemic thrombolysis or, in selected patients, catheter-directed treatment (CDT) procedures, need to be considered [1]. Although systemic thrombolysis was shown to be effective in reducing PE-related mortality, it is accompanied by a substantial risk of major bleeding [1,2,5,6]. Intracranial hemorrhage (ICH) is the most severe bleeding complication of thrombolysis in light of its high early case fatality or, in survivors, dramatic impact on the patients' long-term quality of life [7].

Although earlier observational studies reported risk factors for major bleeding and ICH, [7–9] it is necessary to provide further evidence from large inpatient populations, since analysis of such real-world data may help to optimize patient selection for reperfusion treatment options and minimize the risk of ICH. Therefore, in the present study we analyzed temporal trends of ICH complications and dissected the contributing risk factors for ICH among different reperfusion treatment groups in the entire nationwide population of patients admitted to the hospital due to acute PE in Germany over a 15-year period.

## 2. Methods

The German nationwide inpatient sample, comprising all hospitalization cases (of any age), was screened for patients admitted due to PE during the years 2005–2020. Because of the sensitive nature of the data collected for this study, requests to access analysis in the dataset from qualified researchers trained in human subject confidentiality protocols may be send to Research Data Center (RDC) of the Federal Statistical Office and the Statistical Offices of the federal states, Wiesbaden, Germany.

Data on all hospitalizations of patients with a main diagnosis of PE (ICD code I26) for the period 2005–2020 were obtained as summarized results from the RDC as previously described (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005–2020, own calculations) [2,10,11]. Patients' main diagnosis is that diagnosis, which is mainly and primarily responsible for patients' hospitalization (admission to the hospital) [11].

Therefore, we included only patients admitted due to acute PE (with a main diagnosis of PE), excluding those admitted due to other reasons who developed PE during their in-hospital stay. Data from hospitalized PE patients were analyzed, stratified by the occurrence (or not) of ICH.

ICH was identified if at least one of the following codes were used: ICD codes I60, I61, I62, G95.10, S06.33, S06.5, S06.6 and OPS-codes 5–012.0, 5–012.2, 5–013.1, 5–013.4, 5–014.1, 5–022.0, 5–022.00, 5–022.01, 5–022.02, 5–022.0×, 5–022.20, 5–022.y, 5–033.2, 5–034.1, 5–034.4, 5–038.0, 8–020.d and/or 8–151.1. In addition, we further categorized ICH events to investigate the incidence and impact of intracerebral hemorrhage (ICD code I61) (Table S1 in the Supplementary material). In addition, we identified all PE patient cases with ICB associated to a trauma (ICD codes S06.33, S06.5, S06.6). PE patients with and without ICH were compared, risk factors for ICH were identified and the impact of ICH on case-fatality was calculated.

Severe PE was defined as tachycardia [ICD-10 codes I47 and R00.0], right ventricular (RV) dysfunction [I26.0], shock [R57] or cardiopulmonary resuscitation [OPS code 8–77]; high-risk PE was defined as presence of shock [R57] and/or cardiopulmonary resuscitation [OPS code 8–77]. The disease and procedure codes used to retrieve hemodynamic instability, systemic thrombolysis, catheter-directed thrombolysis, catheter-directed mechanical thrombectomy, and surgical embolectomy have been previously described [10].

### 2.1. Ethical aspects and study oversight

Since the investigators of the study received aggregated results provided by the RDC but had no direct access to individual patient data, neither approval by ethics committees nor patient informed consent were required in compliance with German law. Our work follows the STrengthening the Reporting of OBservational studies in Epidemiology reporting guidelines (http://www.strobe-statement.org/).

### 2.2. Statistical analysis

Descriptive statistics for the comparison of PE patients with and without occurrence of ICH were provided with median and interquartile range (IQR), or absolute numbers and corresponding percentages. Continuous variables were compared with the use of the Wilcoxon-Whitney *U* test, whereas categorical variables were tested with Fisher's exact or chi [2] test. Logistic regression models were computed to identify associations between patients' characteristics, cardiovascular or VTE risk factors, risk stratification markers of PE, comorbidities, adverse in-hospital events on the one hand and ICH on the other hand. In addition, impact of ICH on case-fatality was also assessed by logistic regression. Results are presented as odds ratios (OR) and related 95 % confidence intervals (CI). Multivariable logistic regression models were adjusted for age, sex, obesity, diabetes mellitus, hyperlipidemia, essential arterial hypertension, cancer, surgery, heart failure, acute and/or chronic kidney disease, coronary artery disease, chronic obstructive pulmonary disease, atrial fibrillation/flutter, and chronic anemia.

The software of SPSS® (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) was used for the computerised data analysis. Only *P* values lower than 0.05 (two-sided) were considered to be statistically significant.

## 3. Results

### 3.1. Frequency of intracranial hemorrhage and temporal trends

Between 2005 and 2020, a total of 816,653 patients were hospitalized due to acute PE in Germany. ICH was recorded in 2516 (0.3 %) patients, being intracerebral bleeding in 1282 (0.2 %). Overall, 84,810 (10.4 %) deaths were recorded during in-hospital course, and of these 961 (1.1 %) were related to ICH (Table 1). In the entire PE cohort, fatal ICH was 0.1 % (961/84810). Among patients with severe PE, ICH occurred in 0.6 % of the cases; of those, intracerebral bleeding occurred in 0.3 % and ICH was fatal in also 0.3 % of the cases. By comparison, ICH rate was 0.18 % in low-risk PE, and fatal ICH in only 0.04 % of the cases. In addition, 436 patient cases with PE and ICH (17.2 %) were associated with a trauma.

The hospitalized patients' median age was slightly above 70 years throughout the observational period (Fig. S1 of the Supplementary material). Annual numbers of PE hospitalizations increased, whereas the proportion of patients suffering ICH remained largely unchanged despite annual fluctuations (Fig. 1A). There was a distinct increase of ICH with increasing age: ICH, intracerebral hemorrhage and fatal ICH all peaked in the age group between 70 and 89 years (Fig. 1B). Annual rates of ICH in patients with severe PE followed a similar pattern as in the entire population with PE (Fig. 1C); on the other hand, ICH incidence was similar in all groups until the eighth decade of life and declined thereafter (Fig. 1D), at least in part due to the less frequent usage of reperfusion treatment in older patients (Fig. S2 of the Supplementary material).

### 3.2. Comparison of PE patients with and without ICH

Patients who suffered ICH were slightly older (74.0 [IQR 64.0–81.0] vs. 72.0 [59.0–80.0] years; $P < 0.001$), with a higher proportion above 70 years (63.3 % vs. 55.1 %, $P < 0.001$). While the prevalence of

**Table 1**
Patients' characteristics, medical history, presentation and outcomes of the included 816,653 patients admitted due to pulmonary embolism (PE) stratified according the occurrence of intracranial hemorrhage (ICH).

| Parameters | Hospitalizations of PE patients without ICH (n = 814,137; 99.7 %) | Hospitalizations of PE patients with ICH (n = 2516; 0.3 %) | P-value |
|---|---|---|---|
| Age, median (IQR) | 72.0 (59.0–80.0) | 74.0 (64.0–81.0) | <0.001 |
| Age ≥ 70 years | 448,975 (55.1 %) | 1593 (63.3 %) | <0.001 |
| Female sex | 437,590 (53.7 %) | 1320 (52.5 %) | 0.197 |
| In-hospital stay (days) | 8.0 (5.0–12.0) | 10.0 (3.0–19.0) | <0.001 |
| Traditional cardiovascular risk factors | | | |
| Obesity | 74,854 (9.2 %) | 184 (7.3 %) | 0.001 |
| Essential arterial hypertension | 351,907 (43.2 %) | 1101 (43.8 %) | 0.588 |
| Diabetes mellitus | 132,249 (16.2 %) | 484 (19.2 %) | <0.001 |
| Hyperlipidemia | 103,210 (12.7 %) | 261 (10.4 %) | 0.001 |
| Pulmonary embolism categorization, risk stratification markers | | | |
| Severe PE | 269,426 (33.1 %) | 1554 (61.8 %) | <0.001 |
| High-risk PE | 49,205 (6.0 %) | 612 (24.3 %) | <0.001 |
| Right ventricular dysfunction | 254,691 (31.3 %) | 1458 (57.9 %) | <0.001 |
| Cardiopulmonary resuscitation | 37,533 (4.6 %) | 428 (17.0 %) | <0.001 |
| Shock | 20,983 (2.6 %) | 329 (13.1 %) | <0.001 |
| Syncope | 20,843 (2.6 %) | 165 (6.6 %) | <0.001 |
| Tachycardia | 19,493 (2.4 %) | 108 (4.3 %) | <0.001 |
| Classical risk factors for venous thromboembolism and presence of deep venous thrombosis and/or thrombophlebitis | | | |
| Cancer | 86,205 (10.6 %) | 232 (9.2 %) | 0.026 |
| Any surgery | 300,585 (36.9 %) | 1226 (48.7 %) | <0.001 |
| Pregnancy | 492 (0.1 %) | 4 (0.2 %) | 0.069 |
| Thrombophilia | 11,304 (1.4 %) | 20 (0.8 %) | 0.011 |
| Deep venous thrombosis and/or thrombophlebitis | 355,535 (43.7 %) | 810 (32.2 %) | <0.001 |
| Comorbidities | | | |
| Charlson Comorbidity Index | 4.0 (2.0–5.0) | 5.0 (4.0–7.0) | <0.001 |
| Coronary artery disease | 92,872 (11.4 %) | 301 (12.0 %) | 0.381 |
| Heart failure | 158,035 (19.4 %) | 688 (27.3 %) | <0.001 |
| Peripheral artery disease | 16,190 (2.0 %) | 48 (1.9 %) | 0.772 |
| Atrial fibrillation/flutter | 97,798 (12.0 %) | 489 (19.4 %) | <0.001 |
| Ischemic stroke | 3915 (0.5 %) | 203 (8.1 %) | <0.001 |
| Chronic obstructive pulmonary disease | 69,129 (8.5 %) | 165 (6.6 %) | 0.001 |
| Acute and/or chronic kidney disease | 147,071 (18.1 %) | 694 (27.6 %) | <0.001 |
| Chronic anemia | 45,658 (5.6 %) | 200 (7.9 %) | <0.001 |

classical risk factors for VTE, deep vein thrombosis and/or thrombophlebitis was lower in PE patients with ICH, they exhibited an aggravated comorbidity profile characterized by higher Charlson Comorbidity Index (CCI, 5.0 [4.0–7.0] vs. 4.0 [2.0–5.0]; $P < 0.001$), which was driven, among others, by distinctly higher rates of heart failure ($P < 0.001$) and acute and/or chronic kidney diseases ($P < 0.001$; Table 1).

Patients with ICH more often suffered from severe PE (61.8 % vs. 33.1 %; $P < 0.001$) and high-risk PE (24.3 % vs. 6.0 %; $P < 0.001$). Of PE patients who (later on) developed an ICH, 26.6 % were treated with systemic thrombolysis, 2.3 % with CDT and 1.2 % with surgical embolectomy.

### 3.3. Risk factors for ICH

Older age was an independent risk factor for ICH in the entire study population but not in the subgroup of patients with severe PE (Table 2). Accordingly, patients above the median age of 72 years exhibited almost throughout the observation period an elevated ICH risk compared to younger individuals, in the entire PE population (Fig. 2A). In addition, a higher CCI score was consistently associated with an increased risk for ICH regardless of PE severity (Fig. 2B, Table 2, Tables S2 and S3 of the Supplementary material).

Ischemic stroke was an independent risk factor for ICH development in the multivariate regression model, being associated with a high risk of ICH occurrence both in the general cohort (OR, 14.64 [95%CI 12.61–17.00], $P < 0.001$) and in the subgroup with severe PE (OR, 11.88 [9.97–14.17], $P < 0.001$). In addition, and as shown in Table 2, kidney failure encompassing acute and/or chronic kidney disease (and especially acute kidney injury [OR 3.60 (3.09–4.18), $P < 0.001$]) exhibited an increased risk for ICH. Regarding cardiac diseases, heart failure and atrial fibrillation/flutter were independently associated with ICH occurrence, whereas cancer was not associated with an increased ICH occurrence (Table 2, Fig. 2).

Severe PE and all singular investigated risk stratification markers of PE were identified as risk factors for ICH (Table 2). While there was an increased penetration of CDT use over time, especially in patients with severe PE, the annual numbers of ICH constantly declined over the observation period (Fig. 3). In patients treated with systemic thrombolysis, ICH occurred in 1.8 % of all PE patients and 1.9 % in patients with severe PE. This incidence of ICH in PE patients treated with systemic thrombolysis was widely constant over time (Fig. S3 of the Supplementary material).

### 3.4. Risk factors across different treatment groups

In patients with PE undergoing reperfusion treatment, ICH risk factors varied among different treatment groups (Tables S2 and S3 of the Supplementary material). Systemic thrombolysis was the only reperfusion treatment which showed age- and sex-differences regarding ICH occurrence; female sex ($P = 0.001$) and age ≥ 70 years ($P = 0.009$) were independently associated with increased risk for ICH (Table S2, Fig. S3 of the Supplementary material). Ischemic stroke (OR, 6.26 [4.74–8.27]; $P < 0.001$) was also related to ICH in patients with systemic thrombolysis (Table S2 of the Supplementary material). In PE patients treated with surgical thrombectomy, the risk of ICH was higher when heart failure (OR 2.230 [1.017–4.890]; $P = 0.045$) and/or ischemic stroke (OR 11.72 [4.59–29.94]; $P < 0.001$) were present.

### 3.5. Impact of ICH on case-fatality and other adverse in-hospital events

In-hospital case-fatality was substantially increased in PE patients with ICH (38.2 % vs. 10.3 %; $P < 0.001$) and in the subgroup of patients with intracerebral bleeding (46.0 % vs. 10.3 %; $P < 0.001$) compared to PE patients without such events; the OR for in-hospital death was 6.16 (5.64–6.72; $P < 0.001$ (Table S4). The impact of ICH on case-fatality rate was highest in the second and third decade of life and in the second and third CCI class (Table S5). In addition, we aimed to detect the different impact of ICH driven by traumatic and non-traumatic reasons: both, traumatic and non-traumatic ICH were independently associated with increased case-fatality. Nevertheless, PE patients with non-traumatic ICH had a higher risk to die during in-hospital stay. While traumatic ICH was associated with an increased case-fatality in PE patients (univariable regression: OR 2.31 [1.84–2.91], $P < 0.001$; multivariable regression: OR 2.13 [1.67–2.72]; $P < 0.001$), ICH due to non-traumatic reasons was associated with a substantially higher risk to die univariable regression: OR 6.14 [5.63–6.69], $P < 0.001$; multivariable regression: OR 7.36 [6.70–8.08]; $P < 0.001$).

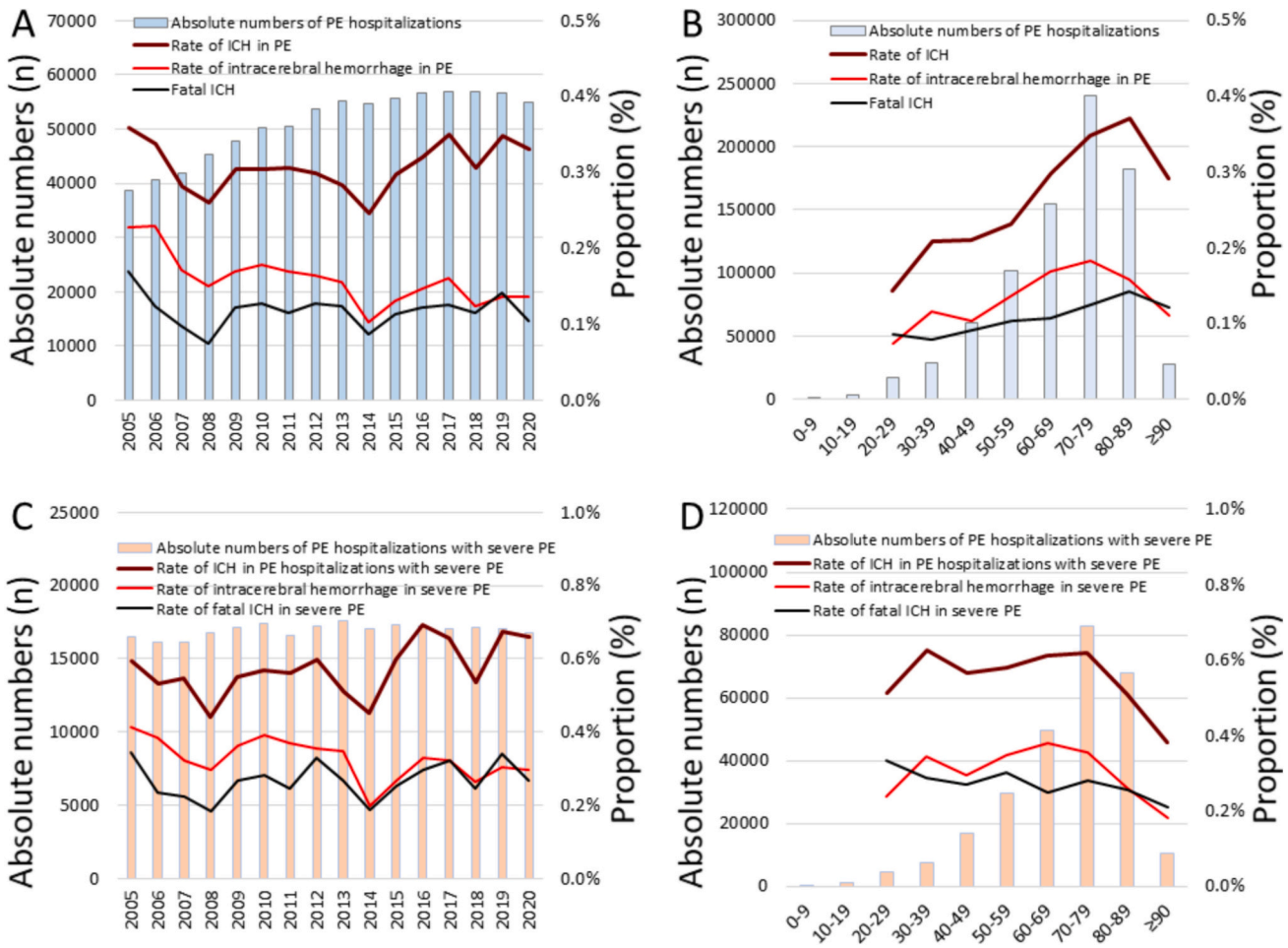


**Fig. 1.** Temporal trends of intracranial hemorrhage (ICH), intracerebral hemorrhage and fatal ICH in all patients admitted due to PE (A, B) and in PE patients with severe PE (C, D).

## 4. Discussion

Bleeding complications and especially ICH remain the most severe adverse events in the acute phase of PE, and the physicians' fear of ICH is a key contributor to the underutilization of various thrombolytic therapies in severe and high-risk PE [2,7,12,13]. Analyzing the large German nationwide inpatient sample with real-world health-care data including all patients with a primary diagnosis of PE, we found that the incidence of ICH, including intracerebral hemorrhage, was overall low and in agreement with results of previously published studies [8,14,15]. Nevertheless, the fact that ICH was independently associated with a 5-fold elevation of in-hospital case-fatality in PE patients underlines the importance of assessing the risk for ICH for proper treatment selection and tailored monitoring.

Several bleeding models have been tested for VTE patients to predict the risk of major bleeding, including the Venous Thromboembolic Disease & Bleeding (VTE-BLEED) [16]. In these models age, active cancer, renal insufficiency, anemia, and a medical history of hypertension or of previous bleeding were identified as the most important predictive variables for ICH. Our analysis showed that PE patients with ICH were older and had an aggravated comorbidity-profile mirrored by a higher CCI. Interestingly, we found no association between cancer and an increased incidence of ICH, most likely as the result of patient selection for reperfusion treatment and thus, this elevated burden was mainly attributed to the higher rates of kidney diseases, atrial fibrillation, heart failure and ischemic stroke. The patients' CCI class has been shown to significantly affect the case fatality and the rates of major adverse events in PE patients irrespective of hemodynamic instability [17]. In line with this previously published paper of our research group, we detected that higher comorbidity burden detected by CCI class was predictive for ICH occurrence in PE patients. The fact that in addition to a higher comorbidity burden, PE patients with ICH exhibited more frequently signs of RV dysfunction, shock and the need of cardiopulmonary resuscitation, contributes additionally to their higher in-hospital deaths and adverse events rates.

A previously developed score suggested a strong association between a medical history of prior stroke and the risk of ICH when thrombolytic treatment is given [7]. Although data about any prior stroke were not available in the RDC, our analysis showed that PE patients with a concomitant ischemic stroke had the highest risk of ICH. In stroke patients, hemorrhagic transformation after thrombolytic treatment for an ischemic stroke is the most serious complication, with an incidence ranging between 2 % and 7 % [18]. While various contributing factors have been recognized in these stroke patients, such as older age, stroke severity and size, uncontrolled hypertension, renal disease, atrial fibrillation or other anticoagulant use, post-thrombolytic hemorrhagic transformation may occur against a complex background of underlying abnormalities such as anticoagulation-induced coagulopathy, reperfusion-related brain injury and blood-brain barrier disruption [18]. In particular atrial fibrillation has recognized as a risk factor for thrombolysis associated ICH, since it may lead to larger volume and more severe ischemic strokes, particularly in an older population [19].

Prevalence of atrial fibrillation/flutter in patients with PE is higher than in the general population, affecting approximately one fifth of PE

**Table 2**
Risk factors for ICH in all 816,653 and in severe 270,980 pulmonary embolism patients.

| Parameters | Pulmonary embolism (n = 816,653) | | | | Severe pulmonary embolism (n = 270,980) | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable regression model | | Multivariable regression model[a] | | Univariable regression model | | Multivariable regression model[a] | |
| | OR (95 % CI) | P-value | OR (95 % CI) | P-value | OR (95 % CI) | P-value | OR (95 % CI) | P-value |
| Age | 1.012 (1.009–1.015) | <0.001 | 1.007 (1.004–1.010) | <0.001 | 0.996 (0.993–0.999) | 0.012 | 0.993 (0.990–0.997) | <0.001 |
| Age ≥ 70 years | 1.404 (1.294–1.522) | <0.001 | 1.226 (1.121–1.341) | <0.001 | 0.928 (0.839–1.027) | 0.148 | 0.870 (0.779–0.971) | 0.013 |
| Female sex | 0.950 (0.878–1.027) | 0.197 | 0.877 (0.809–0.950) | 0.001 | 0.945 (0.855–1.045) | 0.269 | 0.962 (0.868–1.065) | 0.454 |
| Obesity | 0.779 (0.671–0.906) | 0.001 | 0.778 (0.668–0.907) | 0.001 | 0.751 (0.627–0.899) | 0.002 | 0.688 (0.572–0.827) | <0.001 |
| Severe PE | 3.266 (3.013–3.540) | <0.001 | 3.087 (2.843–3.352) | <0.001 | 0.953 (0.860–1.055) | 0.350 | 0.978 (0.880–1.088) | 0.686 |
| Right ventricular dysfunction | 3.027 (2.796–3.277) | <0.001 | 2.861 (2.638–3.102) | <0.001 | | | | |
| Syncope | 2.671 (2.280–3.130) | <0.001 | 2.439 (2.080–2.860) | <0.001 | 1.796 (1.450–2.225) | <0.001 | 1.755 (1.417–2.175) | <0.001 |
| Tachycardia | 1.828 (1.507–2.218) | <0.001 | 1.649 (1.357–2.002) | <0.001 | | | | |
| Cancer | 0.858 (0.749–0.982) | 0.026 | 0.823 (0.718–0.943) | 0.005 | 0.684 (0.560–0.836) | <0.001 | 0.649 (0.531–0.794) | <0.001 |
| Any surgery | 1.624 (1.501–1.756) | <0.001 | 1.585 (1.465–1.716) | <0.001 | 1.812 (1.640–2.002) | <0.001 | 1.802 (1.628–1.994) | <0.001 |
| Pregnancy | 2.633 (0.984–7.050) | 0.054 | 4.216 (1.562–11.382) | 0.005 | 3.860 (1.431–10.410) | 0.008 | 3.160 (1.158–8.621) | 0.025 |
| Comorbidities | | | | | | | | |
| Charlson Comorbidity Index | 1.256 (1.239–1.272) | <0.001 | – | – | 1.178 (1.158–1.199) | <0.001 | – | – |
| Charlson Comorbidity Index class | 2.492 (2.349–2.645) | <0.001 | – | – | 1.912 (1.779–2.054) | <0.001 | – | – |
| Coronary artery disease | 1.055 (0.935–1.191) | 0.381 | 0.877 (0.773–0.995) | 0.042 | 0.904 (0.770–1.060) | 0.215 | 0.873 (0.739–1.032) | 0.111 |
| Heart failure | 1.563 (1.431–1.706) | <0.001 | 1.287 (1.171–1.415) | <0.001 | 1.046 (0.939–1.165) | 0.415 | 0.965 (0.861–1.081) | 0.540 |
| Atrial fibrillation/flutter | 1.767 (1.601–1.951) | <0.001 | 1.451 (1.307–1.612) | <0.001 | 1.305 (1.149–1.481) | <0.001 | 1.297 (1.135–1.482) | <0.001 |
| Ischemic stroke | 18.163 (15.682–21.037) | <0.001 | 2.172 (1.661–2.840) | <0.001 | 13.935 (11.723–16.564) | <0.001 | 11.882 (9.965–14.168) | <0.001 |
| Acute and/or chronic kidney disease | 1.728 (1.583–1.886) | <0.001 | 1.464 (1.331–1.610) | <0.001 | 1.425 (1.278–1.589) | <0.001 | 1.452 (1.292–1.632) | <0.001 |

[a] Adjusted for age, sex, obesity, diabetes mellitus, hyperlipidemia, essential arterial hypertension, cancer, surgery, heart failure, acute and/or chronic kidney disease, coronary artery disease, chronic obstructive pulmonary disease, atrial fibrillation/flutter, and chronic anemia.

patients. Both entities share common risk factors [20,21]. Studies suggest that atrial fibrillation may have a negative impact on patient survival [20,22], although the pathomechanisms by which it may affect the prognosis of PE are not fully elucidated. Randomized controlled trials on anticoagulation in atrial fibrillation reported an ICH rate of 0.8–2.5 %, with non-vitamin K antagonist (direct) oral anticoagulants exhibiting lower incidence of ICH. The strong association between atrial fibrillation/flutter and ICH observed in our study may be explained from the fact that patients with this arrhythmia may also suffer from other cardiovascular comorbidities; besides, they are often already on anticoagulation treatment and therefore bear an elevated risk of major bleeding events [23].

ICH risk factors varied across the different reperfusion treatment groups. Renal disease was deemed to be a risk factor for ICH in all treatment groups except for surgical embolectomy. Recent data from the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study and the UK Biobank reported an independent association of chronic kidney disease or end-stage renal disease with ICH, along with poorer neurological functional outcomes following an ICH [24]. Individuals with chronic kidney disease cannot properly regulate sodium levels and exhibit strong sympathetic activation, leading to hypertension and related complications. Moreover, the elevated urea levels have been shown to jeopardize the endothelial integrity of the cerebral vessels and cause platelet dysfunction [25], which in combination with the elevated blood pressure may facilitate a spontaneous or anticoagulation-induced ICH [24]. On the other hand, while the risk of acute kidney injury in the setting of ICH is well known [26], the risk of ICH in acute kidney disease has not been studied to the same extent [27]. In general, studies have shown that compared to otherwise healthy individuals, patients with acute kidney injury experienced more often a life-threatening bleeding [28].

Systemic thrombolysis was the only reperfusion treatment in our study in which an age and sex dependency was demonstrated, with higher ICH occurrence in female and older patients. Evidence from two meta-analyses suggested that in patients with acute PE, who were treated with systemic thrombolysis, older age was associated with an increased risk of major bleeding [6,29]. Previously developed scores highlighted the importance of age as a predictor of major bleeding as well as of ICH respectively [5,7]. In addition, a recent publication analyzing European data showed that female sex has an increased risk major bleeding [8], while a large multicentre thrombolysis trial, in which tenecteplase was accompanied by higher rates of ICH, indicated that both female sex and increased age (>75 years) may increase the risk of major bleeding [30]. In line with our findings, no sex-dependence regarding major bleeding was detected for catheter-directed thrombolysis in one nationwide study [15], whereas another identified higher bleeding risk for female patients with PE undergoing percutaneous thrombectomy [31]. Notably, the annual rate of ICH in PE patients treated with systemic thrombolysis (1.8 %) is similar to the symptomatic ICH rate reported in recent clinical trials on thrombolytic treatment of

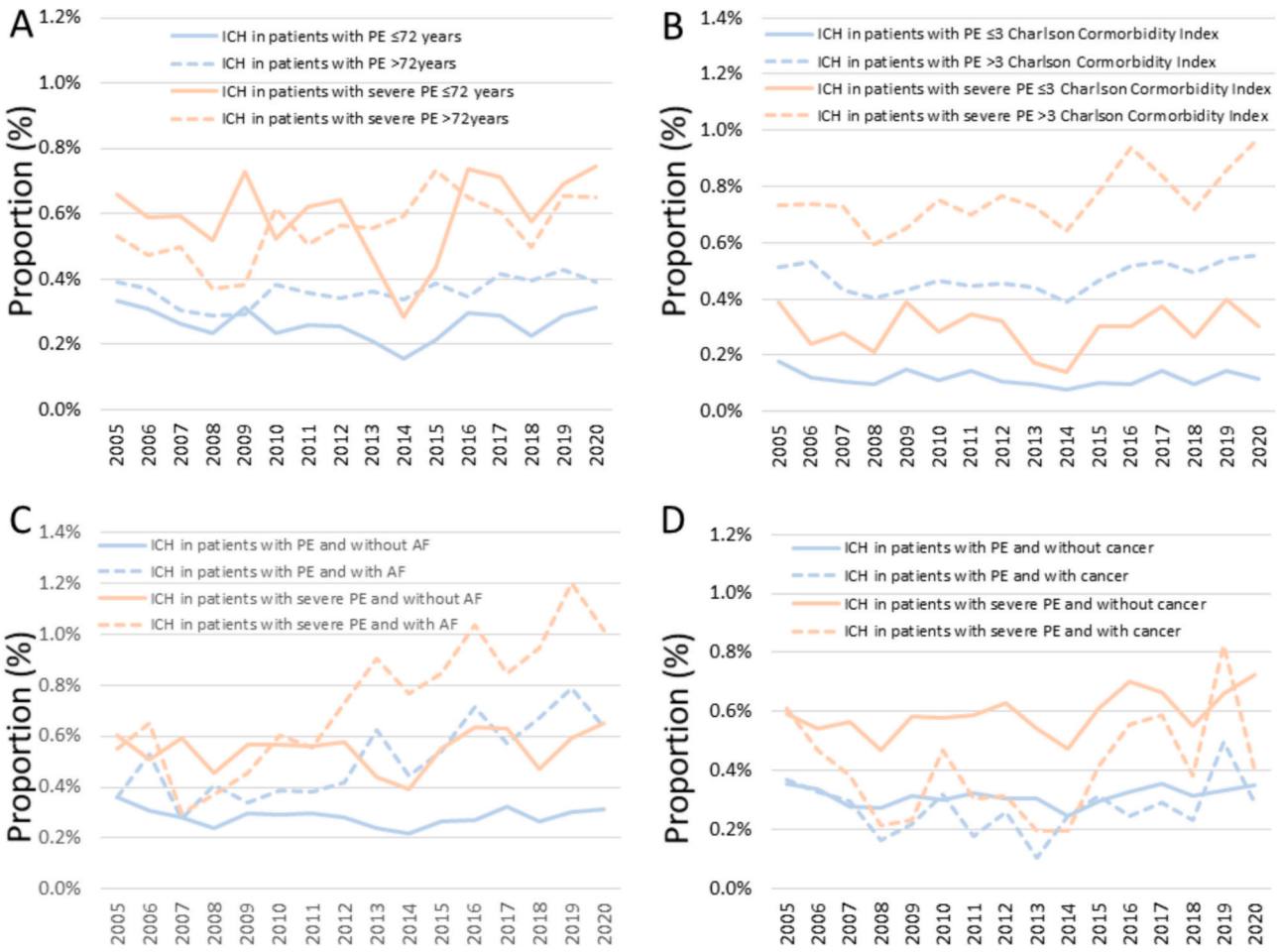


**Fig. 2.** Temporal trends of intracranial hemorrhage (ICH) in all patients admitted due to PE (blue lines) and in PE patients with severe PE (orange lines).
A: prevalence of ICH stratified by median age (≤72 years vs >72 years).
B: prevalence of ICH stratified by median Charlson Cormorbidity Index (CCI, CCI ≤3 vs. CCI >3).
C: prevalence of ICH stratified for presence of atrial fibrillation/flutter (AF).
D: prevalence of ICH stratified for presence of cancer. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

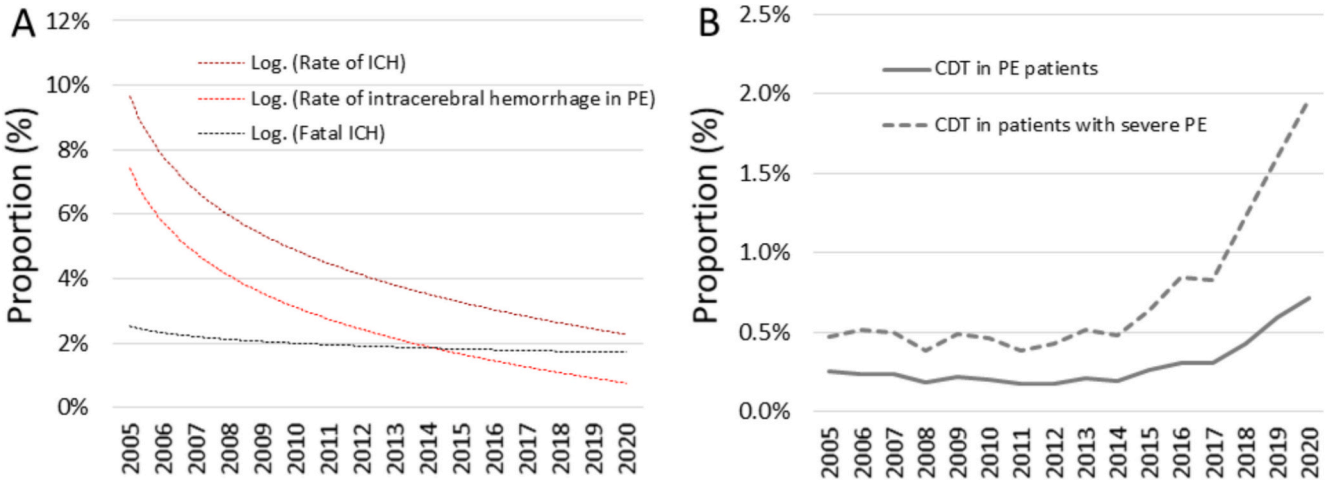


**Fig. 3.** Temporal trends in catheter-directed treatments and intracranial bleeding in PE patients treated with catheter-directed treatments.
A: Annual trends regarding proportion of intracranial hemorrhage in all patients admitted due PE with trend lines (dashed lines).*
B: Annual trends regarding usage of catheter-directed treatments in all hospitalized PE patients (solid grey line) and in patients with severe PE (dashed grey line).
*In some of the years data for ICH were not provided due to data protection.

ischemic stroke [32–34].

Our study supports previous findings showing that despite the increased penetration of CDT use in the treatment of PE (particular in patients with severe PE), the annual trends indicate a decreasing proportion of ICH [35,36]. Since the evidence on the safety of CDT is based predominantly on observational studies, high-quality evidence from large randomized trials is needed to verify these results [37,38].

Some limitations of our present study need consideration. First, the study results are based on disease and procedure codes of hospitalized patients, which may be prone to under-reporting or undercoding. Second, information on anticoagulation strategies (heparins, DOACs, warfarin, phenprocoumon) others than reperfusion strategies used during hospitalization are not part of the dataset of the German nationwide inpatient sample. Third, due to the administrative nature of the data, valid information regarding patients' prior stroke history is not available in this data set. In addition, we were not able to provide data for the long-term follow-up, since only data for hospitalizations were included.

In conclusion, overall incidence of ICH in PE patients treated in Germany largely depended on patients' comorbidity burden. Identifying patients with a high ICH risk will allow better patient selection for different reperfusion treatments in acute PE.

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## CRediT authorship contribution statement

**Konstantinos C. Christodoulou:** Writing - review & editing, Writing - original draft, Conceptualization. **Katharina Mohr:** Writing – review & editing. **Timo Uphaus:** Writing – review & editing, Conceptualization. **Max Jägersberg:** Writing – review & editing, Conceptualization. **Luca Valerio:** Writing – review & editing. **Ioannis T. Farmakis:** Writing – review & editing. **Thomas Münzel:** Writing – review & editing. **Philipp Lurz:** Writing – review & editing. **Stavros V. Konstantinides:** Writing – review & editing, Investigation, Conceptualization. **Lukas Hobohm:** Writing – review & editing, Project administration, Investigation, Conceptualization. **Karsten Keller:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

KCC, KM, TU, MJ, LV, ITF, TM, KK report no conflicts of interests. PL has received institutional fees and research grants from Abbott Vascular, Edwards Lifesciences, and ReCor, honoraria from Edwards Lifesciences, Abbott Medical, Innoventric, ReCor and Boehringer Ingelheim and has stock options with Innoventric. SK reports institutional grants and personal lecture/advisory fees from Bayer AG, Daiichi Sankyo, and Boston Scientific; institutional grants from Inari Medical; and personal lecture/advisory fees from MSD and Bristol Myers Squibb/Pfizer. LH received lecture/consultant fees from MSD and Actelion, outside the submitted work.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2024.109168.

## References

[1] S.V. Konstantinides, G. Meyer, C. Becattini, H. Bueno, G.J. Geersing, V.P. Harjola, M.V. Huisman, M. Humbert, C.S. Jennings, D. Jimenez, et al., 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS), Eur. Heart J. 41 (2020) 543–603, https://doi.org/10.1093/eurheartj/ehz405.

[2] K. Keller, L. Hobohm, M. Ebner, K.P. Kresoja, T. Munzel, S.V. Konstantinides, M. Lankeit, Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany, Eur. Heart J. 41 (2020) 522–529, https://doi.org/10.1093/eurheartj/ehz236.

[3] I. Sagoschen, B. Scibior, I.T. Farmakis, K. Keller, D. Graafen, E.V. Griemert, M. Vosseler, H. Treede, T. Munzel, M. Knorr, et al., A multidisciplinary pulmonary embolism response team (PERT): first experience from a single center in Germany, Clin. Res. Cardiol. (2023), https://doi.org/10.1007/s00392-023-02364-4.

[4] B. Bikdeli, Y. Wang, D. Jimenez, S.A. Parikh, M. Monreal, S.Z. Goldhaber, H. M. Krumholz, Pulmonary embolism hospitalization, readmission, and mortality rates in US older adults, 1999-2015, JAMA 322 (2019) 574–576, https://doi.org/10.1001/jama.2019.8594.

[5] L. Jara-Palomares, D. Jimenez, B. Bikdeli, A. Muriel, P. Rali, Y. Yamashita, T. Morimoto, T. Kimura, R. Le Mao, A. Riera-Mestre, et al., Derivation and validation of a clinical prediction rule for thrombolysis-associated major bleeding in patients with acute pulmonary embolism: the BACS score, Eur. Respir. J. (2020), https://doi.org/10.1183/13993003.02336-2020.

[6] S. Chatterjee, A. Chakraborty, I. Weinberg, M. Kadakia, R.L. Wilensky, P. Sardar, D. J. Kumbhani, D. Mukherjee, M.R. Jaff, J. Giri, Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis, JAMA 311 (2014) 2414–2421, https://doi.org/10.1001/jama.2014.5990.

[7] S. Chatterjee, I. Weinberg, R.W. Yeh, A. Chakraborty, P. Sardar, M.D. Weinberg, C. Kabrhel, G.D. Barnes, D. Mukherjee, D. Kumbhani, et al., Risk factors for intracranial haemorrhage in patients with pulmonary embolism treated with thrombolytic therapy development of the PE-CH score, Thromb. Haemost. 117 (2017) 246–251, https://doi.org/10.1160/TH16-07-0588.

[8] A.C. Mavromanoli, D. Jimenez, O. Sanchez, B. Sobkowicz, S. Vanni, M. Kurzyna, C. Becattini, P. Pruszczyk, H. Wilkens, C. Bova, et al., Major in-hospital bleeding in patients with pulmonary embolism treated with systemic thrombolysis, Thromb. Res. 231 (2023) 29–31, https://doi.org/10.1016/j.thromres.2023.09.009.

[9] F.A. Klok, S. Barco, S.V. Konstantinides, Evaluation of VTE-BLEED for predicting intracranial or fatal bleeding in stable anticoagulated patients with venous thromboembolism, Eur. Respir. J. (2018) 51, https://doi.org/10.1183/13993003.00077-2018.

[10] K. Mohr, L. Hobohm, K. Kaier, I.T. Farmakis, L. Valerio, S. Barco, C. Abele, T. Munzel, T. Neusius, S. Konstantinides, et al., Drivers and recent trends of hospitalisation costs related to acute pulmonary embolism, Clin. Res. Cardiol. (2024), https://doi.org/10.1007/s00392-024-02437-y.

[11] Internet page of the InEK GmbH – Institut für das Entgeltsystem im Krankenhaus vanO. Deutsche Kodierrichtlinien 2018 Druckversion A4 (PDF). https://wwwg-drgde/inek_site_de/layout/set/standard/Media/Files/G-DRG-System/G-DRG-System_2018/Deutsche_Kodierrichtlinien_2018_Druckversion_A4_PDF. 2018.

[12] R. Lecumberri, L. Jimenez, P. Ruiz-Artacho, J.A. Nieto, N. Ruiz-Gimenez, A. Visona, A. Skride, F. Moustafa, J. Trujillo, M. Monreal, et al., Prediction of major bleeding in anticoagulated patients for venous thromboembolism: comparison of the RIETE and the VTE-BLEED scores, TH Open. 5 (2021) e319–e328, https://doi.org/10.1055/s-0041-1729171.

[13] P.D. Stein, F. Matta, Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused, Am. J. Med. 125 (2012) 465–470, https://doi.org/10.1016/j.amjmed.2011.10.015.

[14] S. Arora, S.S. Panaich, N. Ainani, V. Kumar, N.J. Patel, B. Tripathi, P. Shah, N. Patel, S. Lahewala, A. Deshmukh, et al., Comparison of in-hospital outcomes and readmission rates in acute pulmonary embolism between systemic and catheter-directed thrombolysis (from the National Readmission Database), Am. J. Cardiol. 120 (2017) 1653–1661, https://doi.org/10.1016/j.amjcard.2017.07.066.

[15] L. Hobohm, F.P. Schmidt, T. Gori, I. Schmidtmann, S. Barco, T. Munzel, M. Lankeit, S.V. Konstantinides, K. Keller, In-hospital outcomes of catheter-directed thrombolysis in patients with pulmonary embolism, Eur. Heart J. Acute Cardiovasc. Care 10 (2021) 258–264, https://doi.org/10.1093/ehjacc/zuaa026.

[16] F.A. Klok, V. Hosel, A. Clemens, W.D. Yollo, C. Tilke, S. Schulman, M. Lankeit, S. V. Konstantinides, Prediction of bleeding events in patients with venous thromboembolism on stable anticoagulation treatment, Eur. Respir. J. 48 (2016) 1369–1376, https://doi.org/10.1183/13993003.00280-2016.

[17] K. Keller, V.H. Schmitt, O. Hahad, C. Espinola-Klein, T. Munzel, P. Lurz, S. Konstantinides, L. Hobohm, Categorization of patients with pulmonary embolism by Charlson comorbidity index, Am. J. Med. (2024), https://doi.org/10.1016/j.amjmed.2024.04.025.

[18] S. Yaghi, J.Z. Willey, B. Cucchiara, J.N. Goldstein, N.R. Gonzales, P. Khatri, L. J. Kim, S.A. Mayer, K.N. Sheth, L.H. Schwamm, et al., Treatment and outcome of hemorrhagic transformation after intravenous alteplase in acute ischemic stroke: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 48 (2017) e343–e361, https://doi.org/10.1161/STR.0000000000000152.

[19] N.E. Vinding, S.L. Kristensen, R. Rorth, J.H. Butt, L. Ostergaard, J.B. Olesen, C. Torp-Pedersen, G.H. Gislason, L. Kober, C. Kruuse, et al., Ischemic stroke severity and mortality in patients with and without atrial fibrillation, J. Am. Heart Assoc. 11 (2022) e022638, https://doi.org/10.1161/JAHA.121.022638.

[20] K. Ptaszynska-Kopczynska, I. Kiluk, B. Sobkowicz, Atrial fibrillation in patients with acute pulmonary embolism: clinical significance and impact on prognosis, Biomed. Res. Int. 2019 (2019) 7846291, https://doi.org/10.1155/2019/7846291.
[21] K. Keller, J.H. Prochaska, M. Coldewey, S. Gobel, A. Ullmann, C. Junger, H. Lamparter, L. Ariza, C. Bickel, M. Lauterbach, et al., History of deep vein thrombosis is a discriminator for concomitant atrial fibrillation in pulmonary embolism, Thromb. Res. 136 (2015) 899–906, https://doi.org/10.1016/j.thromres.2015.08.024.
[22] B. Bikdeli, M.D. Abou Ziki, G.Y.H. Lip, Pulmonary embolism and atrial fibrillation: two sides of the same coin? A systematic review. Semin Thromb Hemost. 43 (2017) 849–863, https://doi.org/10.1055/s-0036-1598005.
[23] N. van Rein, U. Heide-Jorgensen, W.M. Lijfering, O.M. Dekkers, H.T. Sorensen, S. C. Cannegieter, Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy, Circulation 139 (2019) 775–786, https://doi.org/10.1161/CIRCULATIONAHA.118.036248.
[24] K.N. Vanent, A.C. Leasure, J.N. Acosta, L.R. Kuohn, D. Woo, S.B. Murthy, H. Kamel, S.R. Messe, M.T. Mullen, J.B. Cohen, et al., Association of chronic kidney disease with risk of intracerebral hemorrhage, JAMA Neurol. 79 (2022) 911–918, https://doi.org/10.1001/jamaneurol.2022.2299.
[25] P. Boccardo, G. Remuzzi, M. Galbusera, Platelet dysfunction in renal failure, Semin. Thromb. Hemost. 30 (2004) 579–589, https://doi.org/10.1055/s-2004-835678.
[26] S. She, Y. Shen, K. Luo, X. Zhang, C. Luo, Prediction of acute kidney injury in intracerebral hemorrhage patients using machine learning, Neuropsychiatr. Dis. Treat. 19 (2023) 2765–2773, https://doi.org/10.2147/NDT.S439549.
[27] F. Zarka, A. Tayler-Gomez, T. Ducruet, A. Duca, M. Albert, A. Bernier-Jean, J. Bouchard, Risk of incident bleeding after acute kidney injury: a retrospective cohort study, J. Crit. Care 59 (2020) 23–31, https://doi.org/10.1016/j.jcrc.2020.05.003.
[28] M. Ma, W.D. Gao, Y.F. Gu, Y.S. Wang, Y. Zhu, Y. He, Clinical effects of acute kidney injury after transcatheter aortic valve implantation: a systematic review and meta-analysis, Intern. Emerg. Med. 14 (2019) 161–175, https://doi.org/10.1007/s11739-018-1935-6.
[29] C. Marti, G. John, S. Konstantinides, C. Combescure, O. Sanchez, M. Lankeit, G. Meyer, A. Perrier, Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis, Eur. Heart J. 36 (2015) 605–614, https://doi.org/10.1093/eurheartj/ehu218.
[30] G. Meyer, E. Vicaut, T. Danays, G. Agnelli, C. Becattini, J. Beyer-Westendorf, E. Bluhmki, H. Bouvaist, B. Brenner, F. Couturaud, et al., Fibrinolysis for patients with intermediate-risk pulmonary embolism, N. Engl. J. Med. 370 (2014) 1402–1411, https://doi.org/10.1056/NEJMoa1302097.
[31] M.A. Agarwal, J.S. Dhaliwal, E.H. Yang, O. Aksoy, M. Press, K. Watson, B. Ziaeian, G.C. Fonarow, J.M. Moriarty, R. Saggar, et al., Sex differences in outcomes of percutaneous pulmonary artery thrombectomy in patients with pulmonary embolism, Chest 163 (2023) 216–225, https://doi.org/10.1016/j.chest.2022.07.020.
[32] Y. Xiong, B.C.V. Campbell, L.H. Schwamm, X. Meng, A. Jin, M.W. Parsons, M. Fisher, Y. Jiang, F. Che, L. Wang, et al., Tenecteplase for ischemic stroke at 4.5 to 24 hours without thrombectomy, N. Engl. J. Med. 391 (2024) 203–212, https://doi.org/10.1056/NEJMoa2402980.
[33] S.B. Coutts, S. Ankolekar, R. Appireddy, J.F. Arenillas, Z. Assis, P. Bailey, P. A. Barber, R. Bazan, B.H. Buck, K.S. Butcher, et al., Tenecteplase versus standard of care for minor ischaemic stroke with proven occlusion (TEMPO-2): a randomised, open label, phase 3 superiority trial, Lancet 403 (2024) 2597–2605, https://doi.org/10.1016/S0140-6736(24)00921-8.
[34] G.W. Albers, M. Jumaa, B. Purdon, S.F. Zaidi, C. Streib, A. Shuaib, N. Sangha, M. Kim, M.T. Froehler, N.E. Schwartz, et al., Tenecteplase for stroke at 4.5 to 24 hours with perfusion-imaging selection, N. Engl. J. Med. 390 (2024) 701–711, https://doi.org/10.1056/NEJMoa2310392.
[35] K. Mohr, B. Keeling, K. Kaier, T. Neusius, R.P. Rosovsky, J.M. Moriarty, K. Rosenfield, C. Abele, I.T. Farmakis, K. Keller, et al., Modelling costs of interventional pulmonary embolism treatment: implications of US trends for a European healthcare system, Eur. Heart J. Acute Cardiovasc. Care (2024), https://doi.org/10.1093/ehjacc/zuae019.
[36] A.K. Pasha, M.U. Siddiqui, M.D. Siddiqui, A. Ahmed, A. Abdullah, I. Riaz, M. H. Murad, H. Bjarnason, W.E. Wysokinski, R.D. McBane 2nd, Catheter directed compared to systemically delivered thrombolysis for pulmonary embolism: a systematic review and meta-analysis, J. Thromb. Thrombolysis 53 (2022) 454–466, https://doi.org/10.1007/s11239-021-02556-7.
[37] P. Pruszczyk, F.A. Klok, N. Kucher, M. Roik, N. Meneveau, A.S.P. Sharp, J. E. Nielsen-Kudsk, S. Obradovic, S. Barco, F. Giannini, et al., Percutaneous treatment options for acute pulmonary embolism: a clinical consensus statement by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function and the European Association of Percutaneous Cardiovascular Interventions, EuroIntervention 18 (2022) e623–e638, https://doi.org/10.4244/EIJ-D-22-00246.
[38] R. Chopard, N. Meneveau, F. Ecarnot, Catheter-based therapy for acute pulmonary embolism: an overview of current evidence, Arch. Cardiovasc. Dis. 115 (2022) 397–405, https://doi.org/10.1016/j.acvd.2022.06.001.