# Prognostic impact of copeptin in pulmonary embolism: a multicentre validation study

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**Copeptin improves risk stratification of normotensive patients with pulmonary embolism** http://ow.ly/8E3P30jtvym

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ABSTRACT To externally validate the prognostic impact of copeptin, either alone or integrated in risk stratification models, in pulmonary embolism (PE), we performed a *post hoc* analysis of 843 normotensive PE patients prospectively included in three European cohorts.

Within the first 30 days, 21 patients (2.5%, 95% CI 1.5–3.8) had an adverse outcome and 12 (1.4%, 95% CI 0.7–2.5) died due to PE. Patients with copeptin ⩾24 pmol·L$^{-1}$ had a 6.3-fold increased risk for an adverse outcome (95% CI 2.6–15.5, p<0.001) and a 7.6-fold increased risk for PE-related death (95% CI 2.3–25.6, p=0.001). Risk classification according to the 2014 European Society of Cardiology (ESC) guideline algorithm identified 248 intermediate-high-risk patients (29.4%) with 5.6% (95% CI 3.1–9.3) at risk of adverse outcomes. A stepwise biomarker-based risk assessment strategy (based on high-sensitivity troponin T, N-terminal pro-brain natriuretic peptide and copeptin) identified 123 intermediate-high-risk patients (14.6%) with 8.9% (95% CI 4.5–15.4) at risk of adverse outcomes. The identification of patients at higher risk was even better when copeptin was measured on top of the 2014 ESC algorithm in intermediate-high-risk patients (adverse outcome OR 11.1, 95% CI 4.6–27.1, p<0.001; and PE-related death OR 13.5, 95% CI 4.2–43.6, p<0.001; highest risk group *versus* all other risk groups). This identified 85 patients (10.1%) with 12.9% (95% CI 6.6–22.0) at risk of adverse outcomes and 8.2% (95% CI 3.4–16.2) at risk of PE-related deaths.

Copeptin improves risk stratification of normotensive PE patients, especially when identifying patients with an increased risk of an adverse outcome.

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## Introduction

The 2014 guideline of the European Society of Cardiology (ESC) recommends risk stratification of patients with acute pulmonary embolism (PE), because this can influence treatment decisions [1]. While haemodynamically unstable PE patients are easily identified as being at high risk, risk stratification in initially normotensive PE is more challenging. A multimodal approach based on a clinical risk prediction score (*e.g.* the simplified Pulmonary Embolism Severity Index (sPESI) [2]), testing of cardiac biomarkers and imaging of the right ventricle is proposed to classify normotensive patients into low, intermediate-low or intermediate-high-risk groups [1]. However, this ESC algorithm is complex and may be insufficient to identify higher risk patients who potentially may profit from a more aggressive treatment strategy. Thus, in the past years, several attempts have been made to optimise risk stratification in normotensive PE [3–6].

Right ventricular (RV) dysfunction due to the sudden increase of RV afterload is considered a critical determinant of PE severity, because it can lead to a decreased left ventricular preload and, subsequently, to shock. While cardiac biomarkers such as high-sensitivity troponin T (hsTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) reflect myocardial injury or stretch [7, 8], vasopressin (AVP), and its more stable surrogate marker copeptin, might reflect a promising new pathophysiological axis of PE severity because AVP is released on stress and hypotension and may therefore indicate impaired haemodynamics due to RV failure [9, 10]. In a prospective single-centre derivation study including 268 normotensive PE patients [9], we showed that elevated copeptin levels using an optimal cut-off value of 24 pmol·L$^{-1}$ were associated with a 5.4-fold increased risk of an adverse 30-day outcome. The odds ratio for an adverse outcome was even higher if copeptin was combined with the cardiac biomarkers hsTnT and NT-proBNP in a stepwise biomarker-based risk assessment strategy.

The aim of the present European multicentre study was to validate the prognostic impact of copeptin in normotensive PE. In particular, we aimed to validate a stepwise biomarker-based risk assessment strategy combining cardiac biomarkers and copeptin and to investigate the prognostic impact of copeptin for the identification of normotensive PE patients at higher risk of an adverse 30-day outcome.

## Methods

### *Patient population and study design*

At each cooperating site (provided in the supplementary material), consecutive patients aged ⩾18 years with objectively confirmed acute symptomatic PE were prospectively enrolled in local ongoing non-interventional cohort studies. For the present *post hoc* analysis, only normotensive (systolic blood pressure ⩾90 mmHg on admission) patients were included. Patients with missing blood samples, invalid biomarker measurements and German patients previously included in the derivation study [9] were excluded from analysis. All sites followed the same study protocol (as described in [7]), allowing the patient cohorts to be pooled. Information on the definitions used in the present study are provided in the supplementary material.

Patients were stratified to risk classes according to the sPESI [2], 2014 ESC algorithm [1], biomarker-based risk assessment strategy [9] and Bova score [3]; missing values were considered to be normal.

The primary outcome was an adverse 30-day outcome, defined as PE-related death or at least one of the following complications: need for 1) catecholamine administration, 2) mechanical ventilation or 3) cardiopulmonary resuscitation. The secondary outcomes were defined as PE-related or all-cause death within 30 days. All outcomes, including causes of death, were adjudicated by local independent adjudication committees. Death was determined to be PE-related if it was either confirmed by autopsy or followed a clinically severe episode of acute PE in the absence of an alternative diagnosis.

The study was conducted in accordance with the amended Declaration of Helsinki; the study protocol was approved by the local independent ethics committees of each participating site and all patients gave written informed consent. Treatment decisions were made by the physicians caring for the patients and were not influenced by the study protocol. Study results were not communicated to the treating physicians and thus not used to guide the patients' management or to monitor the effects of treatment at any time.

### *Laboratory biomarker testing*

Venous blood samples were collected on admission and immediately stored at −80°C. Plasma levels of copeptin, hsTnT and NT-proBNP were measured *post hoc* as described previously [9] and in the supplementary material. Elevated biomarker concentrations were prospectively defined as hsTnT ⩾14 pg·mL$^{-1}$ [7], NT-proBNP ⩾600 pg·mL$^{-1}$ [8] and copeptin ⩾24 pmol·L$^{-1}$ [9].

### *Statistical analysis*

Analyses were performed using SPSS (version 23.0; SPSS Inc., Chicago, IL, USA). Categorical variables are presented as n (%); study outcomes are given as absolute risk (%) with corresponding 95% confidence intervals calculated using Clopper–Pearson "exact" intervals. Comparison of categorical variables was performed with Fisher's exact test. The Kolmogorov–Smirnov test revealed that continuous variables did not follow a normal distribution. They are therefore presented as median (interquartile range (IQR)). The Mann–Whitney U-test was used for comparison of continuous variables. Receiver operating characteristics (ROC) analysis was performed and the area under the curve (AUC) determined to test the performance of copeptin with regard to the prediction of an adverse outcome and PE-related death. Youden's index quantification was used to identify the optimal cohort-specific cut-off values. Univariable logistic regression analysis was used to calculate the odds ratio and the corresponding 95% confidence intervals of variables with regard to the prediction of an adverse outcome and of PE-related death. For this purpose, risk models (2014 ESC algorithm, Bova score, biomarker-based strategy, modified 2014 ESC algorithm and 2014 ESC algorithm with subsequent copeptin measurement in intermediate-high-risk patients) were dichotomised by testing patients classified in the highest risk group *versus* patients stratified in any other risk group (combination of low-risk and intermediate-low-risk class). Additionally, parameters univariably associated with an adverse outcome were separately tested in combination with copeptin $\geqslant$24 pmol·L$^{-1}$ in multivariable logistic regression models. Sensitivity, specificity, negative predictive values, positive predictive values, negative and positive likelihood ratios and the corresponding 95% confidence intervals were calculated. All statistical tests were two-sided and used a significance level of 0.05.

TABLE 1 Baseline characteristics, medical history and initial presentation of the study patients

| | All study patients | Copeptin <24 pmol·L$^{-1}$ | Copeptin $\geqslant$24 pmol·L$^{-1}$ | p-value |
|---|---|---|---|---|
| **Subjects N** | 843 | 662 | 181 | |
| **Age years median (IQR)** | 70.0 (53.0–79.0), n=841 | 67.0 (50.0–77.0), n=661 | 77.0 (67.0–82.5), n=180 | <0.001 |
| **Female** | 408 (48.4) | 323 (48.8) | 85 (47.0) | 0.676 |
| **BMI kg·m$^{-2}$ median (IQR)** | 26.8 (24.0–30.0), n=620 | 26.7 (23.7–30.1), n=483 | 27.0 (24.4–30.0), n=137 | 0.357 |
| **Comorbidities** | | | | |
| Active cancer | 126 (15.0), n=842 | 95 (14.4), n=662 | 31 (17.2), n=180 | 0.347 |
| Chronic heart failure | 61 (7.2), n=842 | 30 (4.5), n=662 | 31 (17.2), n=180 | <0.001 |
| Chronic pulmonary disease | 89 (10.6), n=842 | 63 (9.5), n=662 | 26 (14.4), n=180 | 0.074 |
| Renal insufficiency | 244 (29.2), n=836 | 159 (24.1), n=659 | 85 (48.0), n=177 | <0.001 |
| **Symptoms** | | | | |
| Signs/symptoms of DVT | 221 (26.2) | 189 (28.5) | 32 (17.7) | 0.003 |
| Chest pain | 365 (43.3), n=842 | 300 (45.4), n=661 | 65 (35.9), n=181 | 0.028 |
| Dyspnoea | 645 (76.6), n=842 | 501 (75.8), n=661 | 144 (79.6), n=181 | 0.322 |
| Syncope | 133 (15.8), n=842 | 89 (13.5), n=661 | 44 (24.3), n=181 | 0.001 |
| **Haemodynamic status at presentation** | | | | |
| Mild hypotension | 34 (4.1), n=830 | 20 (3.1), n=654 | 14 (8.0), n=176 | 0.008 |
| Tachycardia | 309 (37.1), n=834 | 221 (33.7), n=656 | 88 (49.4), n=178 | <0.001 |
| Hypoxia | 135 (19.7), n=687 | 89 (16.5), n=539 | 46 (31.1), n=148 | <0.001 |
| RV dysfunction (on TTE) | 195 (25.5), n=766 | 142 (23.2), n=611 | 53 (34.2), n=155 | 0.007 |
| RV dysfunction (on TTE or MDCT) | 267 (32.9), n=811 | 192 (30.1), n=638 | 75 (43.4), n=173 | 0.001 |
| **Laboratory biomarkers** | | | | |
| hsTnT pg·mL$^{-1}$ median (IQR) | 19.3 (7.9–44.7) | 14.7 (6.6–35.2) | 40.7 (24.3–84.2) | <0.001 |
| hsTnT $\geqslant$14 pg·mL$^{-1}$ | 504 (59.8) | 344 (52.0) | 160 (88.4) | <0.001 |
| NT-proBNP pg·mL$^{-1}$ median (IQR) | 449 (115–2257) | 290 (95–1342) | 1787 (431–7246) | <0.001 |
| NT-proBNP $\geqslant$600 pg·mL$^{-1}$ | 376 (44.6) | 250 (37.8) | 126 (69.6) | <0.001 |
| **Risk classes** | | | | |
| sPESI $\geqslant$1 point | 495 (58.7) | 348 (52.6) | 147 (81.2) | <0.001 |
| **2014 ESC algorithm#** | | | | |
| Low risk | 135 (16.0) | 126 (19.0) | 9 (5.0) | <0.001 |
| Intermediate-low risk | 460 (54.6) | 373 (56.3) | 87 (48.1) | 0.053 |
| Intermediate-high risk | 248 (29.4) | 163 (24.6) | 85 (47.0) | <0.001 |

Data are presented as n (%), unless otherwise stated. n refers to the number of patients with available data. IQR: interquartile range; BMI: body mass index; DVT: deep vein thrombosis; RV: right ventricular; TTE: transthoracic echocardiography; MDCT: multidetector computed tomography; hsTnT: high-sensitivity troponin T; NT-proBNP: N-terminal pro-brain natriuretic peptide; sPESI: simplified Pulmonary Embolism Severity Index; ESC: European Society of Cardiology. #: according to the 2014 ESC algorithm, patients with a sPESI of 0 points and elevated hsTnT or NT-proBNP plasma concentrations were reclassified to the intermediate-low risk category.

## Results

### *Study cohort and patient outcomes*

Between August 2007 and May 2016, 883 patients were included in the study; of those, 30 were excluded because of missing blood samples and 10 because of invalid biomarker measurements. Thus, 843 normotensive PE patients (496 from Spain, 252 from Poland and 95 from Germany) were included in the present analysis. The medical history and baseline characteristics of the study patients are provided in table 1. An echocardiographic examination was performed in 766 patients (90.9%); of those, 195 (25.5% of patients with transthoracic echocardiography (TTE), 23.1% of all patients) were diagnosed with RV dysfunction. During the first 30 days, the primary outcome (adverse 30-day outcome) occurred in 21 patients (2.5%, 95% CI 1.5–3.8), all-cause death in 36 patients (4.3%, 95% CI 3.0–5.9) and PE-related death in 12 patients (1.4%, 95% CI 0.7–2.5).

### *Prognostic impact of copeptin in normotensive PE*

Copeptin plasma concentrations ranged from 1.0 to 380.1 pmol·L$^{-1}$ (median 9.6 pmol·L$^{-1}$, IQR 5.2–21.1). Differences of patients with copeptin levels above the predefined cut-off value of 24 pmol·L$^{-1}$ compared to patients with copeptin levels <24 pmol·L$^{-1}$ are shown in table 1. The median copeptin concentrations were higher in patients with an adverse outcome or PE-related death than in patients with a favourable outcome (32.7 pmol·L$^{-1}$, IQR 8.8–52.3 *versus* 9.5 pmol·L$^{-1}$, IQR 5.2–20.4, p<0.001; and 31.5 pmol·L$^{-1}$, IQR 9.3–64.8 *versus* 9.5 pmol·L$^{-1}$, IQR 5.2–20.7, p<0.001) and more patients with an adverse outcome or PE-related death had copeptin ⩾24 pmol·L$^{-1}$ (61.9%, 95% CI 38.4–81.9 *versus* 20.4%, 95% CI 17.7–23.4, p<0.001; and 66.7%, 95% CI 34.9–90.1 *versus* 20.8%, 95% CI 18.1–23.7, p=0.001) compared to patients with a favourable clinical course. Patients with copeptin ⩾24 pmol·L$^{-1}$ more often had an adverse outcome (7.2%, 95% CI 3.9–12.0 *versus* 1.2%, 95% CI 0.5–2.4; p<0.001) or died of PE (4.4%, 95% CI 1.9–8.5 *versus* 0.6%, 95% CI 0.2–1.5; p=0.001) compared to patients with copeptin <24 pmol·L$^{-1}$. The prognostic performance of copeptin and other risk assessment tools with regard to an adverse outcome are shown in table 2. Using ROC analysis, the AUC for copeptin was 0.70 (95% CI 0.57–0.83, p=0.002) for predicting an adverse outcome and 0.71 (95% CI 0.55–0.88, p=0.011) for predicting PE-related death. In comparison, the AUC for predicting an adverse outcome for hsTnT was 0.69 (95% CI 0.58–0.79, p=0.004) and for NT-proBNP was 0.72 (95% CI 0.58–0.85, p=0.001) (figure 1). In univariate logistic regression analysis, copeptin ⩾24 pmol·L$^{-1}$ was associated with a more than six-fold increased risk of an adverse outcome and an almost eight-fold increased risk for PE-related death (table 3). Further univariable predictors of primary or secondary study outcomes are shown in table 3. The prognostic value of copeptin ⩾24 pmol·L$^{-1}$ to predict an adverse outcome or PE-related death remained independent if tested with each variable associated with these outcomes separately in multivariable logistic models (data not shown). Similar results were obtained if patient cohorts of the derivation [9] and the present studies were pooled (supplementary material).

### *Copeptin helps to identify normotensive PE patients with an elevated risk for adverse outcomes*

Using a simple stepwise biomarker-based strategy, 504 patients (59.8%) were classified as low risk with a rate of an adverse outcome of 1.0% (95% CI 0.3–2.3) (figure 2a). Specifically, one patient (0.2% of all low-risk patients) died of PE, three patients required administration of catecholamines and two patients required mechanical ventilation. Using the 2014 ESC algorithm, only 135 patients (16.0%) were classified as low risk; none of them had an adverse outcome (figure 2b). At the other end of the risk spectrum, the 2014 ESC algorithm classified 248 patients (29.4%) as being at intermediate-high risk; of those, 14 (5.6%, 95% CI 3.1–9.3) had an adverse outcome and nine (3.6%, 95% CI 1.7–6.8) died of PE. In comparison,

TABLE 2 Prognostic performance of dichotomised laboratory biomarkers, RV dysfunction according to imaging modalities and sPESI with regard to an adverse 30-day outcome

| | Sensitivity | Specificity | PPV | NPV | LR+[#] | LR−[#] |
|---|---|---|---|---|---|---|
| **hsTnT ⩾14 pg·mL$^{-1}$** | 90 (71–97) | 41 (38–44) | 4 (2–6) | 99 (98–100) | 1.5 (1.3–1.8) | 0.2 (0.1–0.9) |
| **NT-proBNP ⩾600 pg·mL$^{-1}$** | 81 (60–92) | 56 (53–60) | 5 (3–7) | 99 (98–100) | 1.9 (1.5–2.3) | 0.3 (0.1–0.8) |
| **Copeptin ⩾24 pmol·L$^{-1}$** | 62 (41–79) | 80 (77–82) | 7 (4–12) | 99 (98–99) | 3.0 (2.1–4.3) | 0.5 (0.3–0.8) |
| **sPESI ⩾1 point** | 90 (71–97) | 42 (39–45) | 4 (2–6) | 99 (98–100) | 1.6 (1.3–1.8) | 0.2 (0.1–0.8) |
| **RV dysfunction (on TTE)** | 44 (23–67) | 75 (72–78) | 4 (2–7) | 98 (97–99) | 1.7 (1.0–3.1) | 0.8 (0.5–1.2) |
| **RV dysfunction (on TTE or MDCT)** | 48 (28–67) | 67 (64–71) | 4 (2–7) | 98 (96–99) | 1.5 (0.9–2.3) | 0.8 (0.5–1.2) |

Data are presented as % (95% CI), unless otherwise stated. PPV: positive predictive value; NPV: negative predictive value; LR+/−: positive/negative likelihood ratio; hsTnT: high-sensitivity troponin T; NT-proBNP: N-terminal pro-brain natriuretic peptide; sPESI: simplified Pulmonary Embolism Severity Index; RV: right ventricular; TTE: transthoracic echocardiography; MDCT: multidetector computed tomography. [#]: data presented as ratio (95% CI).

patients classified as intermediate-high risk using the biomarker-based strategy had a higher rate of adverse outcomes of 8.9% (95% CI 4.5–15.4) and PE-related deaths of 5.7% (95% CI 2.3–11.4).

To combine the successful performance of the 2014 ESC algorithm in identifying low-risk patients and the more effective identification of normotensive PE patients at higher risk using copeptin, we tested whether copeptin measurement on top of the 2014 ESC algorithm could further improve risk stratification of patients classified as intermediate-high risk. As shown in figure 2c, when using copeptin ⩾24 pmol·L$^{-1}$ to further stratify patients in the intermediate-high-risk group, 85 patients (10.1%) were identified as being at higher risk with a rate of adverse outcome of 12.9% (95% CI 6.6–22.0) and of PE-related death of 8.2% (95% CI 3.4–16.2) while 163 patients were reclassified as intermediate-low risk. Given that not all hospitals will have TTE always available for the assessment of RV dys(function), and evidence of RV dysfunction on TTE was not associated with an increased risk of an adverse outcome in the present study (OR 2.3, 95% CI 0.9–6.3, p=0.099), we tested whether replacing information from imaging modalities with copeptin measurements in the 2014 ESC algorithm could provide comparable prognostic information. These results are shown in supplementary figure 1s.

In summary, the odds ratios determined using logistic regression analysis for risk of adverse outcome or PE-related death, respectively, for patients classified to the highest risk groups based on 1) the biomarker-based strategy (figure 2a) were 7.0 (95% CI 2.9–16.8, p<0.001) and 8.6 (95% CI 2.7–27.6, p<0.001), 2) the 2014 ESC algorithm (figure 2b) were 5.0 (95% CI 2.0–12.6, p=0.001) and 7.4 (95% CI 2.0–27.7, p=0.003), 3) the modified 2014 ESC algorithm (using copeptin instead of imaging in the 2014 ESC algorithm, supplementary figure 1s) were 7.4 (95% CI 3.1–18.0, p<0.001) and 7.6 (95% CI 2.4–24.2, p=0.001) and 4) the 2014 ESC algorithm followed by measurement of copeptin (figure 2c) were 11.1 (95% CI 4.6–27.1, p<0.001) and 13.5 (95% CI 4.2–43.6, p<0.001) (table 3). Figure 3 gives an overview of the percentage of patients with an adverse outcome and PE-related death in each risk class using different risk assessment strategies.

## Discussion

We performed a *post hoc* analysis of a large pooled European multicentre cohort to validate the prognostic impact of copeptin in 843 normotensive patients with acute PE. The main study findings can be summarised as follows: 1) copeptin using a predefined cut-off value of 24 pmol·L$^{-1}$ had a good prognostic performance and was associated with a 6.3-fold increased risk for an adverse outcome and a 7.6-fold increased risk for PE-related death; 2) established risk assessment strategies such as the 2014 ESC algorithm safely identify PE patients at low risk while a stepwise biomarker-based risk assessment strategy combining hsTnT, NT-proBNP and copeptin appears especially useful to identify normotensive PE patients with a higher risk of adverse outcomes; and 3) risk stratification of normotensive PE can be optimised if copeptin is measured on top of the 2014 ESC algorithm.

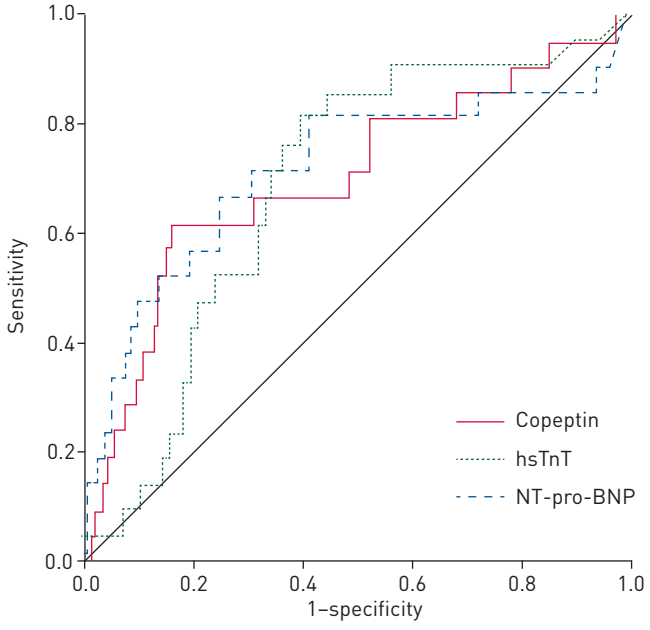


FIGURE 1 Receiver operating characteristics analysis for biomarkers with regard to an adverse 30-day outcome. Area under the curve for copeptin (pmol·L$^{-1}$), high-sensitivity troponin T (hsTnT) (pg·mL$^{-1}$) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (pg·mL$^{-1}$) with regard to an adverse 30-day outcome.

TABLE 3 Predictors of adverse outcomes

| | Adverse 30-day outcome | p-value | PE-related death | p-value | All-cause death | p-value |
|---|---|---|---|---|---|---|
| **Subjects (%, 95% CI)** | 21 (2.5, 1.5–3.8) | | 12 (1.4, 0.7–2.5) | | 36 (4.3, 3.0–5.9) | |
| **Age >75 years** | 8.06 (2.69–24.20) | **<0.001** | 5.55 (1.49–20.65) | **0.011** | 3.37 (1.68–6.76) | **0.001** |
| **Comorbidities** | | | | | | |
| Chronic heart failure | 5.57 (2.08–14.93) | **0.001** | 2.61 (0.56–12.21) | 0.222 | 2.73 (1.09–6.84) | **0.032** |
| Chronic pulmonary disease | 3.56 (1.34–9.42) | **0.011** | 2.88 (0.77–10.86) | 0.117 | 3.54 (1.65–7.61) | **0.001** |
| Active cancer | 0.59 (0.14–2.57) | 0.484 | 0.51 (0.07–4.01) | 0.524 | 3.04 (1.48–6.24) | **0.003** |
| **Symptoms** | | | | | | |
| Chest pain | 0.32 (0.11–0.96) | **0.043** | 1.09 (0.33–3.60) | 0.887 | 0.42 (0.20–0.91) | **0.027** |
| **Laboratory biomarkers** | | | | | | |
| hsTnT $\geqslant$14 pg·mL$^{-1}$ | 6.60 (1.53–28.53) | **0.011** | | | 4.38 (1.69–11.38) | **0.002** |
| NT-proBNP $\geqslant$600 pg·mL$^{-1}$ | 5.48 (1.83–16.43) | **0.002** | 14.04 (1.81–109.28) | **0.012** | 4.62 (2.08–10.25) | **<0.001** |
| Copeptin $\geqslant$24 pmol·L$^{-1}$ | 6.33 (2.58–15.51) | **<0.001** | 7.61 (2.26–25.56) | **0.001** | 4.45 (2.26–8.75) | **<0.001** |
| **Risk classes** | | | | | | |
| sPESI $\geqslant$1 point | 6.91 (1.60–29.84) | **0.010** | 7.89 (1.01–61.37) | **0.049** | | |
| Biomarker-based strategy: intermediate-high risk[#] | 6.97 (2.90–16.80) | **<0.001** | 8.63 (2.69–27.65) | **<0.001** | 6.69 (3.37–13.26) | **<0.001** |
| 2014 ESC algorithm: intermediate-high risk[#] | 5.03 (2.00–12.61) | **0.001** | 7.43 (2.00–27.69) | **0.003** | 3.58 (1.81–7.06) | **<0.001** |
| 2014 ESC algorithm plus copeptin: intermediate-high risk[#] | 11.12 (4.57–27.05) | **<0.001** | 13.52 (4.19–43.59) | **<0.001** | 7.52 (3.71–15.24) | **<0.001** |
| Modified 2014 ESC algorithm: intermediate-high risk[#] | 7.44 (3.07–18.01) | **<0.001** | 7.55 (2.36–24.15) | **0.001** | 5.78 (2.92–11.43) | **<0.001** |

Data are presented as OR (95% CI), unless otherwise stated. Bold font indicates statistical significance. PE: pulmonary embolism; hsTnT: high-sensitivity troponin T; NT-proBNP: N-terminal pro-brain natriuretic peptide; sPESI: simplified Pulmonary Embolism Severity Index; ESC: European Society of Cardiology. [#]: intermediate-high risk tested *versus* intermediate-low and low risk.

### *Validation of the prognostic impact of copeptin in normotensive PE*

Copeptin as a surrogate marker for AVP was identified as a helpful novel biomarker for rapid rule-out of myocardial infarction [11, 12]. Additionally, it has been shown to predict prognosis in acute coronary syndrome [13], chronic heart failure [14, 15], pulmonary hypertension [16] and, recently, acute PE [9, 17, 18]. In heart failure [14, 15], copeptin was superior to natriuretic peptides with regard to the prediction of death. In patients with acute myocardial infarction, Khan *et al.* [13] demonstrated that copeptin was a predictor of death, especially if combined with NT-proBNP. The authors of the latter article underline that "a multimarker strategy […] using independent biomarkers has benefits in that it integrates the different pathways involved, in the hope that complementary information can be gained" [13]. In acute PE, the sudden increase of RV afterload may lead to a decrease in left ventricular preload and subsequently to low cardiac output and shock. Given that AVP, together with copeptin, is released upon stress and hypotension [9, 10], this may reflect a novel pathophysiological axis of PE severity by indicating the systemic response to impaired haemodynamics due to RV failure.

Although the rate of an adverse 30-day outcome was lower in the present study compared to the derivation studies (2.5% in this study compared to 5.6% in [9] and 9.3% in [17]), we were able to validate the prognostic impact of elevated copeptin plasma concentrations. Of note, this direct comparison might be biased given the different endpoint definitions. However, in agreement with the derivation studies, patients with an adverse outcome had higher copeptin plasma concentrations on admission and elevated copeptin levels were associated with a >6-fold increased risk for an adverse outcome (derivation study OR 5.4, 95% CI 1.7–17.6 [9]). In the present study, copeptin was identified as a predictor of PE-related death, supporting the concept that copeptin provides information on the haemodynamic impairment due to acute RV failure (which might require more aggressive treatment regimens) [18]. Importantly, the prognostic value of copeptin remained independent if tested separately with other variables associated with an adverse outcome or PE-related death in multivariable logistic models.

When using a predefined cut-off value of 24 pmol·L$^{-1}$, only 21.5% of the study patients had elevated copeptin, whereas hsTnT and NT-proBNP were elevated in as many as 59.8% and 44.6% of patients, respectively. Thus, and as shown in table 2, hsTnT and NT-proBNP were associated with better sensitivity than copeptin. These biomarkers may therefore be useful to identify low-risk patients, whereas copeptin

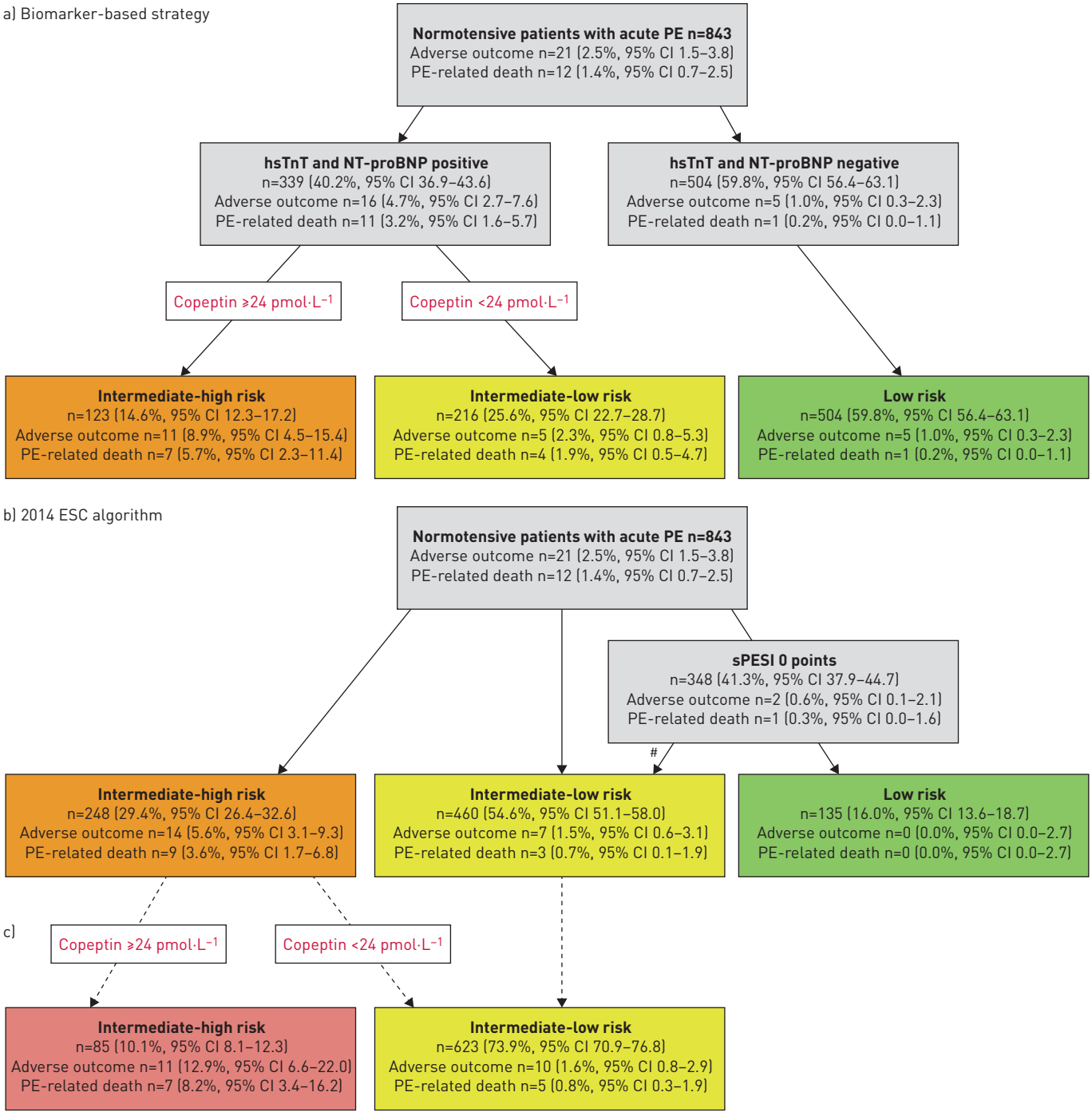


FIGURE 2 Risk assessment strategies for normotensive pulmonary embolism (PE) patients. a) Risk assessment using a biomarker-based strategy based on high-sensitivity troponin T (hsTnT), N-terminal pro-brain natriuretic peptide (NT-proBNP) and copeptin. b) Risk assessment as proposed by the 2014 European Society of Cardiology (ESC) guideline. c) Adding measurement of copeptin in patients classified as intermediate-high risk by the 2014 ESC algorithm helps to identify patients with an increased risk for an adverse outcome. #: according to the 2014 ESC algorithm, patients with a simplified Pulmonary Embolism Severity Index (sPESI) of 0 points and elevated hsTnT or NT-proBNP plasma concentrations were reclassified as intermediate-low risk. A "positive" hsTnT and NT-proBNP test refers to plasma concentrations ⩾14 pg·mL$^{-1}$ and ⩾600 pg·mL$^{-1}$, respectively.

had the highest specificity among all tested variables, which may enable copeptin to identify normotensive PE patients at higher risk. However, as indicated by the moderate individual prognostic performance (figure 1 and table 2), none of the biomarkers should be used alone to risk stratify patients for guidance of therapeutic management.

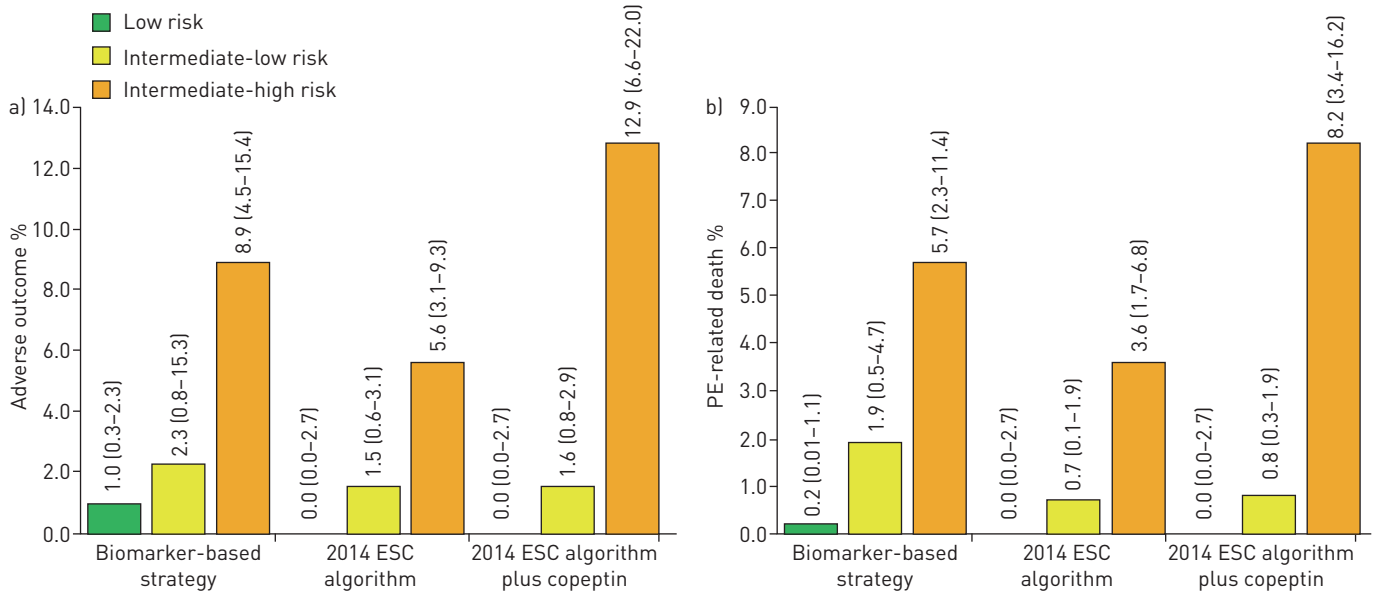


FIGURE 3 Percentage of patients with a) an adverse outcome and b) pulmonary embolism (PE)-related death in each risk category using different risk assessment strategies. All tested strategies were able to stratify patients according to their risk of an adverse outcome and PE-related death. Adding copeptin measurement in intermediate-high-risk patients to the 2014 European Society of Cardiology (ESC) algorithm identified a subgroup of patients with the highest rate of an adverse outcome and PE-related death.

### *A novel stepwise biomarker-based strategy*

Due to the complex and time-, labour- and potentially cost-intensive approach of the algorithm proposed by the 2014 ESC guideline (requiring three steps with calculation of the sPESI, laboratory testing and imaging procedures), we have developed a novel and simple stepwise biomarker-based strategy [9]. In the derivation study, using the biomarker-based approach instead of the 2014 ESC classification [9] classified more patients as low risk, none of whom reached the primary outcome. Additionally, more patients in the intermediate-high-risk group had an adverse outcome [9]. The present multicentre study allows these findings to be validated. The novel stepwise biomarker-based strategy identified a small group of patients at intermediate-high risk (14.6%) with a rate of 8.6% (95% CI 4.5–15.4) of PE-related death or complications (OR 7.0, 95% CI 2.9–16.8, p<0.001; figure 2a). Although this proportion is lower than the rate of 20% of adverse outcomes reported in the derivation study [9], the intermediate-high-risk group still had a higher rate of adverse outcomes when classified by the stepwise biomarker-based strategy rather than by the 2014 ESC algorithm (5.6%, 95% CI 3.1–9.3; OR 5.0, 95% CI 2.0–12.6; p=0.001) or the Bova score (5.4%, 95% CI 1.5–13.3; OR 2.5, 95% CI 0.8–7.7; p=0.104). On the other end of the risk spectrum, as many as 59.8% of patients were classified in the low-risk group using the biomarker-based strategy with an acceptable rate of an adverse outcome (1.0%, 95% CI 0.3–2.3) while only 16% of patients were classified in the low-risk group by the 2014 ESC algorithm; none (95% CI 0.0–2.7) of these patients had an adverse outcome. Of note, because hsTnT and NT-proBNP were measured in all patients, the number of patients reclassified from low risk to intermediate-low risk might have been higher than in real-world scenarios [19]. Although routine performance of imaging or laboratory testing in the presence of a sPESI of 0 is not considered necessary by current ESC guidelines [1], evidence is accumulating that especially younger PE patients with fewer comorbidities might be misclassified as low risk if further assessment of RV (dys)function is withheld [20]. Thus, risk stratification of PE patients for guidance of the therapeutic strategy should be based on an assessment of the disease-specific prognosis (*e.g.* PE-related death or complications) if aiming to identify candidates for thrombolytic therapy, and on an assessment of overall prognosis (*e.g.* by the use of the sPESI [2] or the RIETE score [21]) if aiming to identify candidates for home treatment. Of course, before final therapeutic decisions can be made, the respective treatment-related risks (*e.g.* risk of bleeding when considering thrombolysis or choosing the optimal anticoagulant strategy and risks related to ambulatory care if considering early discharge) should be assessed.

### *Improving risk stratification based on the 2014 ESC algorithm by adding copeptin*

The Pulmonary Embolism Thrombolysis (PEITHO) study [22] demonstrated that the combined primary endpoint of death or haemodynamic decompensation within 7 days can be reduced by 46% by administrating a fibrinolytic therapy to normotensive PE patients with RV dysfunction and troponin

elevation. However, this benefit was achieved at the cost of increased intracranial and major extracranial bleeding [22]. Consequently, the 2014 ESC guideline does not recommend initial thrombolysis in haemodynamically stable PE patients, but does recommend close monitoring of patients in the intermediate-high-risk group to permit early detection of signs of haemodynamic compromise to initiate timely (rescue) thrombolysis [1]. While this recommendation appears to be a reasonable consequence of the results from the PEITHO study and findings from further studies (summarised in [23]), one may be puzzled by the comparably low rate of death and haemodynamic decompensation of 5.6% in the placebo arm of PEITHO. In comparison, recent derivation cohort studies developing combination models for the identification of intermediate-high-risk PE patients reported complication rates of >20% in the high-risk groups (PREP score, 22.2% [24]; FAST score, 20.5% [25]; Bova score, 29.2% [3]). If we assume the same relative risk reduction in these "truly" intermediate-high-risk patients, the risk-to-benefit ratio could be tipped in favour of thrombolytic therapy [26]. Thus, in the present study, we used copeptin $\geqslant$24 pmol·L$^{-1}$ to further identify patients at intermediate-high risk classified by the 2014 ESC algorithm at highest risk (figure 2c). A small group of higher risk patients (10.1% of the overall cohort) with a rate of adverse outcome of 12.9% (95% CI 6.6–22.0) and of PE-related death of 8.2% (95% CI 3.4–16.2) was identified. However, whether intermediate-high-risk patients identified based on copeptin or other combination models will benefit from more aggressive treatment remains to be tested and demonstrated in appropriately designed trials. Of note, and as shown and discussed in the supplementary material and table 3, copeptin can also be used instead of imaging modalities in the 2014 ESC algorithm for risk stratification.

Some limitations deserve consideration: first, the rate of patients with PE-related death (1.4%, 95% CI 0.7–2.5) or PE-related complications (2.5%, 95% CI 1.5–3.8) was lower than in other cohort studies [3, 5] and the derivation studies [9, 17], and below the suggested number of events for external validation of a prognostic model [27, 28]. However, statistical analyses revealed satisfactory results given the large overall patient number and we were able to confirm the prognostic impact of copeptin, alone or integrated in risk assessment strategies, as well as findings from the two derivation studies [9, 17]. Additionally, a pooled analysis of the derivation and the validation cohort with 36 adverse outcomes (3.2%, 95% CI 2.3–4.5) in 1111 patients provided comparable results (shown in the supplementary material). Second, due to the *post hoc* study design and inclusion of patients from 12 sites in three countries, echocardiographic criteria for the definition of RV dysfunction differed (as explained in detail in the supplementary material). But given the lack of an accepted standardised definition of RV dysfunction on TTE in general, this does more likely reflect current practice under real-world conditions rather than a limitation. Finally, acknowledging that the implementation of copeptin in clinical routine may constitute a logistical challenge for laboratories because its measurement requires a separate analyser presumably not available in most (smaller) hospitals, further studies should address the cost-effectiveness of copeptin measurements.

In conclusion, copeptin may improve risk stratification of normotensive PE patients if integrated in a simple stepwise biomarker-based risk assessment strategy (combining different information obtained from hsTnT, NT-proBNP and copeptin) and if measured on top of the 2014 ESC algorithm. Pending confirmation by an adequately designed management trial, copeptin appears especially useful for the identification of normotensive PE patients with a higher risk of PE-related adverse outcomes who might be candidates for more aggressive treatment strategies with a risk-to-benefit ratio in favour of a thrombolytic therapy.

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