Summary

Title: Identification of patients with very low risk acute pulmonary embolism with use of clinical assessment and biomarker concentrations

Introduction: Acute pulmonary embolism (APE) is a common disease, affecting 75-269 out of 100 000 people each year. Clinical spectrum of APE is broad, ranging from asymptomatic or mild dyspnoea to shock and cardiac arrest. Currently, when direct oral anticoagulants (DOAC) are easily accessible, well selected individuals could be treated as outpatients, however, there are no clear criteria to select patients who could be safely treated in ambulatory care. Although there is evidence of the safety and effectiveness of home treatment qualification based on sPESI scale or the Hestia criteria, further analyses showed benefits of combining those with right ventricular dysfunction (RVD) assessment on imaging studies and laboratory biomarker testing (troponins and N-terminal pro B-type natriutetic peptide [NT-proBNP]). Nevertheless, in most facilities skilled echocardiographist may not always be immediately reachable and results of clinical trials regarding RVD assessment in computed tomography in low risk patients remain equivocal.

Aim: The aim of this work was to analyze severe in-hospital APE-related adverse events among patients with sPESI score of 0, to establish criteria allowing to identify very low risk group, that could be safely referred to ambulatory care, based on clinical findings (0 points on the sPESI) and widely available laboratory biomarker tests (troponins and NT-proBNP).

Methods: This is a *post-hoc* analysis of the ongoing prospective observational study "PE-Aware" registered at ClinicalTrials.gov (unique identifier NCT03916302). Data included 1151 adults, consecutive APE patients, managed in a single referral center during the period January 2006–December 2019. Cardiac troponin and NT-proBNP assessment and echocardiographic examination were performed within 24 hours after admission. The clinical endpoint included APE-related mortality and/or clinical deterioration requiring intravenous catecholamines administration, rescue thrombolysis and/or immediate surgical embolectomy.

Results: For the first part (Publication No. 1; Bartosz Karolak et al., „Plasma Troponins Identify Patients with Very Low-Risk Acute Pulmonary Embolism", Journal of Clinical Medicine, 2023;12(4):1276), in the final analysis we included 409 patients with sPESI score of

0. CE occurred in four patients, who had higher serum troponin levels than subjects with favorable clinical course (troponin/ULN: 7.8 (6.4–9.4) vs. 0.2 (0–1.36) $p < 0.001$). Receiver operating characteristic (ROC) analysis showed that the area under the curve for troponin in the prediction of CE was 0.908 (95% CI: 0.831–0.984; $p < 0.001$). We defined the cut-off value of troponin at >1.7 upper level of normal (ULN). In logistic regression, univariate and multivariate analysis showed that elevated plasma troponin level was associated with an increased risk of CE, whereas RV/LV > 1.0 was not.

For the second part (Publication No. 2; Bartosz Karolak et al., „Plasma N-terminal pro-brain natriuretic peptide concentrations may help to identify patients with very low-risk acute pulmonary embolism: A preliminary study", Advances in Clinical and Experimental Medicine, 2024 Online ahead of print) we included 348 patients, for whom NT-proBNP plasma concentrations were available. Clinical endpoints occurred in 3 patients, who had higher plasma NT-proBNP levels than study participants with favorable clinical course (2930 [2285.5–13965] pg/mL vs 164 [64–650] pg/mL p = 0.01). ROC analysis showed that the area under the curve for NT-proBNP for the prediction of the endpoints was 0.918 (95% CI: 0.831–1.00; p = 0.013). We defined the cutoff value of NT-proBNP at 1641 pg/mL.

Conclusions: Solely sPESI score assessment seems to be insufficient to refer patients with APE to ambulatory care. sPESI score of 0 combined with troponin levels not exceeding 1.7 ULN, or alternatively NT-proBNP concentrations below 1641 pg/ml, allow to identify very low risk patients. Due to the single-center nature of the study and low number of endpoints, the results of this analysis should be interpreted with caution. Presented results, and above all the presented threshold values, require further analyzes and external validation.