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Non-recommended dosing of direct oral anticoagulants in the treatment of acute pulmonary embolism is related to an increased rate of adverse events

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Background

- The 2016 ACCP guidelines recommend henceforth DOACs rather than VKA to treat acute VTE
- Dose adjustment is not required in the setting of acute PE treatment according to the manufacturer's labelling, beyond the contraindication in patients with a creatinine clearance (CrCl) < 30 mL/min
- The frequency of prescription of non-recommended DOAC doses, and its impact on outcomes, is poorly described in real-life practice

Aim of the study

- To investigate patterns of prescription of non-recommended DOAC doses for the treatment of acute PE, and the associated risk of 6-month adverse events.

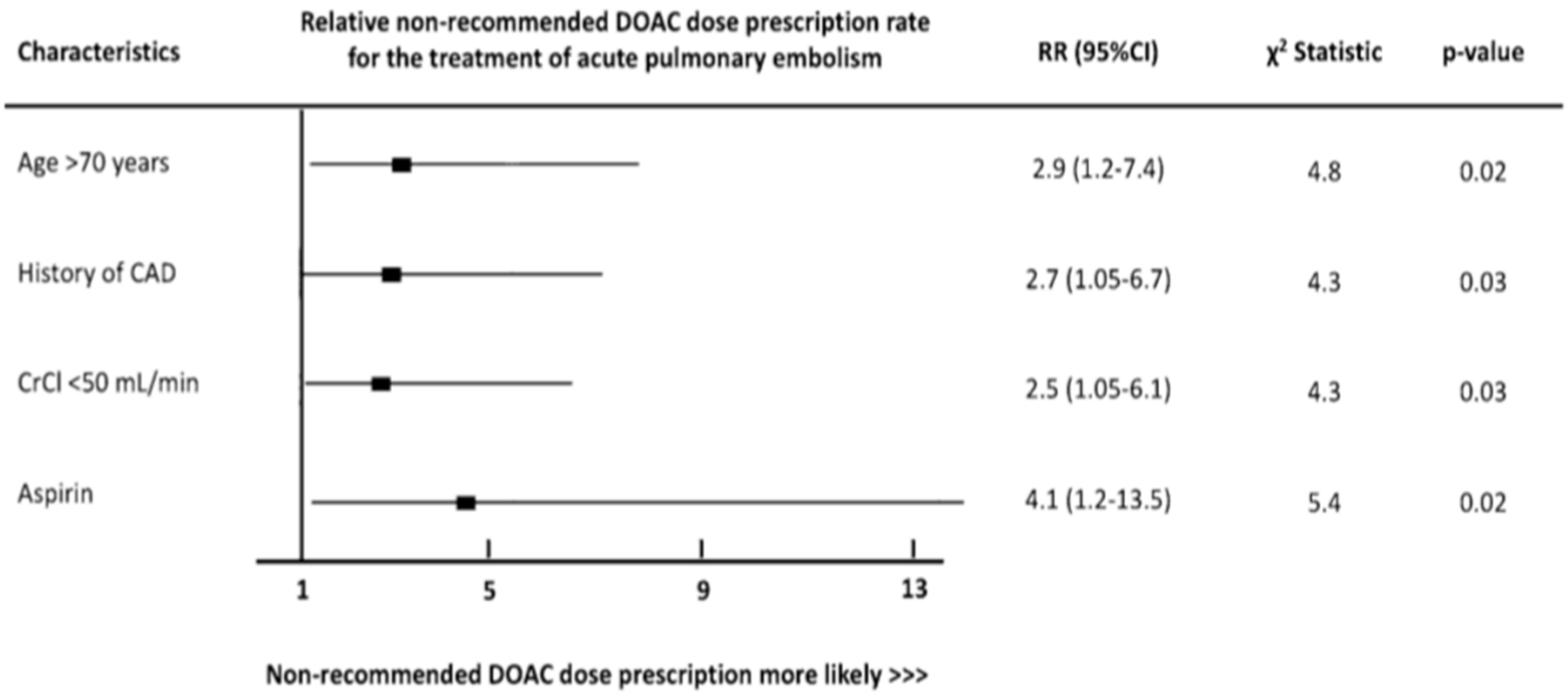
Methods

- Prospective, observational study, based on a multicenter registry
- Inclusion criteria were all patients aged 18 years or older with confirmed PE by computed tomography pulmonary angiography (CTPA), or ventilation–perfusion (V–Q) scan, discharge from hospital with a DOAC therapy
- DOACs studied: rivaroxaban and apixaban
- The primary endpoint: a composite of death from any cause, recurrent VTE, major bleeding, and chronic thromboembolic pulmonary hypertension (CTEPH).
- Follow up: 6 months

Results (I)

- 656 patients: 614 patients (93.6%) treated with rivaroxaban; 42 patients (6.4%) treated with apixaban
- A total of 628 patients (95.7%) were treated with the recommended DOAC dose, and 28 patients (4.3%) had non-recommended DOAC dosing
- By multivariate analysis, age > 70 years (OR 2.9; 95% CI 1.2–7.4), a history of CAD (OR 2.7; 95% CI 1.05–6.7), creatinine clearance < 50 mL/min (OR 2.5; 95% CI 1.05–6.1), and concomitant aspirin therapy (OR 4.1; 95% CI 1.2–13.5) were independent factors associated with non-recommended DOAC prescription

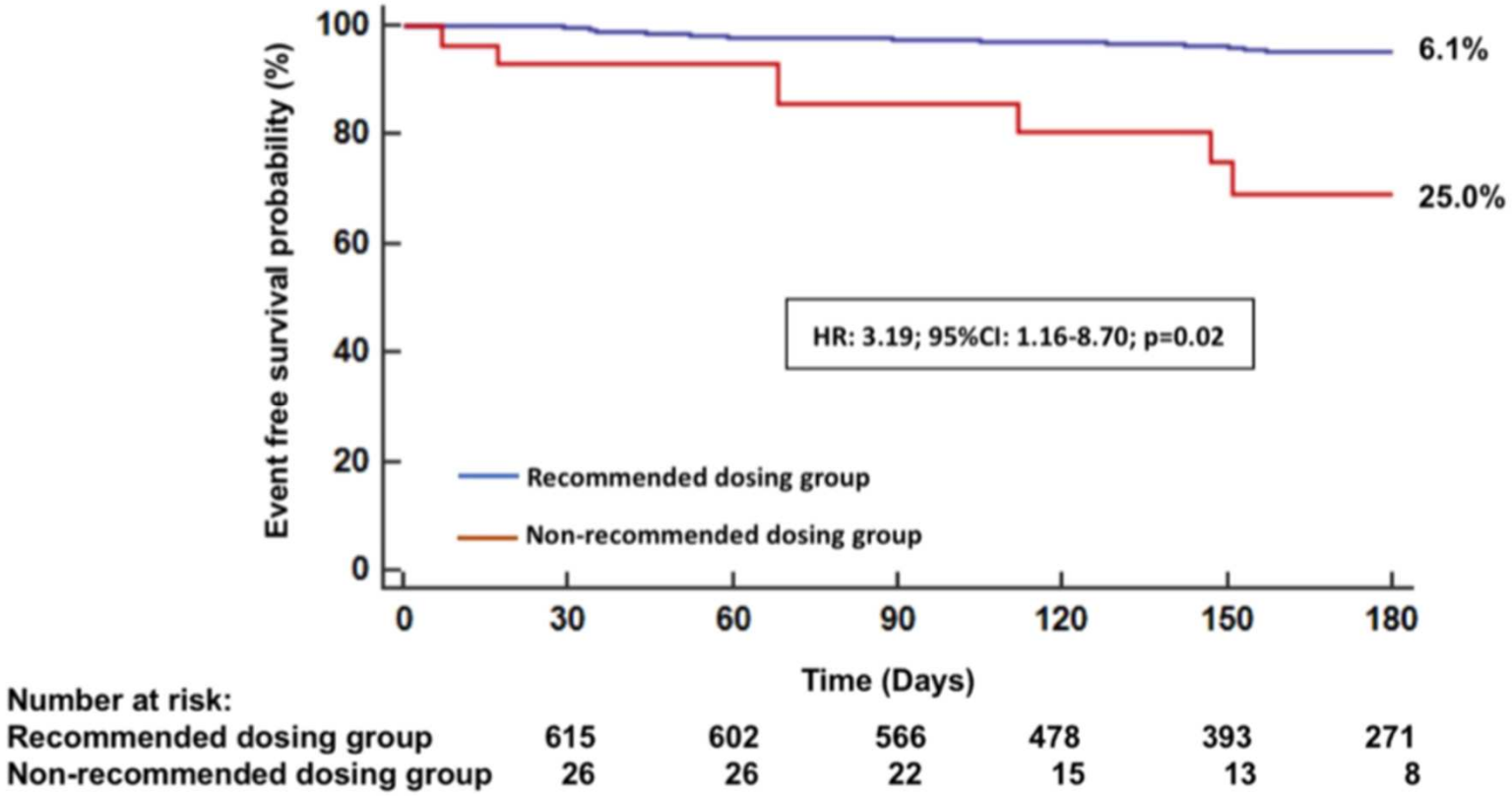
Clinical factors independently associated with the prescription of non-recommended direct oral anticoagulant dose for the treatment of acute pulmonary embolism.



Results (II)

- The primary composite endpoint occurred in 7 patients (25%) in the non-recommended dose group and in 38 patients (6.1%) in the recommended dose group (OR 3.19; 95% CI 1.16–8.70; p = 0.02)
- The higher primary endpoint rate observed in the non-recommended dose group was driven by a significantly higher rate of major bleeding (7.1 vs. 1.4%; p = 0.008), and a non-significant trend toward higher rate of death (7.1 vs. 2.2%, p = 0.23), recurrent VTE (3.6 vs. 1.4%, p = 0.31), and CTEPH (7.1 vs. 1.6%, p = 0.32)

Kaplan–Meier curves of 6-month survival free from the combined primary endpoint in the recommended and non-recommended direct oral anticoagulant dose prescription groups for the treatment of acute pulmonary embolism.



Number at risk:						
Recommended dosing group	615	602	566	478	393	271
Non-recommended dosing group	26	26	22	15	13	8

Discussion

- 4.3% of patients treated with DOACs for the treatment of acute PE did not receive an appropriate dose at discharge
- Older age, CAD on aspirin, and renal function impairment were factors associated with off-label DOAC prescription by providers
- The rate of adverse events at 6 months after PE diagnosis was significantly higher in the group of patients inappropriately treated with DOACs as compared to those who assumed the appropriate dose
- This higher rate of adverse events was driven by a significantly higher rate of major bleeding and by numerically albeit non-significantly higher rates of death, recurrent VTE, and CTEPH
- Our findings emphasize the provider's concerns about DOAC prescription and bleeding risk: however, the use of an off-label dose of DOAC did not lead to a reduction in the risk of bleeding