

Terapie anticoagulanti e gestione delle complicanze

CORRELATION BETWEEN DIRECT ORAL ANTICOAGULANTS PLASMA LEVELS AND BRAIN VASCULAR EVENTS

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Background and Aims. The reference ranges of direct oral anticoagulants (DOACs) plasma concentrations demonstrate a high intra- and inter-individual variability. Many studies reported an association between DOACs plasma levels and the risk of thrombotic and bleeding events. The aim of this single-center retrospective observational study was to assess the relationship between DOACs plasma levels measured at the time of acute ischemic stroke or intracerebral hemorrhage (ICH) in patients on DOAC for atrial fibrillation (AF) or venous thromboembolism (VTE).

Methods. The study analyzed 206 patients presented to the emergency department of Maggiore Hospital, Bologna, between November 2022 and July 2025 for acute ischemic stroke (150 patients) or ICH (56 patients) on DOAC at recommended doses for AF-related stroke prevention or VTE prevention, with dose adjustment when indicated, and adherent to treatment. Patients mean age was 80 years (47.1% female) and mean CHA2DS2-VA score was 3.7. 42.2% of patients was on low dose DOAC treatment. Blood samples for DOACs plasma level measurement were collected at the time of emergency room admission. The analysis was performed categorizing DOAC plasma levels into quartiles across the entire population and per single DOAC, calculating the median (IQR) with approximately equal group size.

Results. A significant association was observed between DOAC plasma levels and the type of cerebral event. The proportion of ischemic stroke progressively decreased across increasing quartiles (90.6% in Q1, 72.5% in Q2, 64.0% in Q3 and 63.5% in Q4, p=0.004), whereas ICH showed the opposite trend, increasing from 9.4% in Q1 to 36.5% in Q4 (p=0.004). These trends were observed even calculating the percentages of quartiles distribution of DOACs plasma levels for each single DOAC (figure). In the multivariable logistic regression model the Q1 of DOAC plasma levels, calculated either across the entire population or per single DOAC, was strongly associated with the outcome (OR 3.16, 95% CI 1.26-7.92, p=0.014 and OR 4.83, 95% CI 1.75-13.3, p=0.002 respectively), indicating that patients with the lowest drug concentrations had approximately three/four-fold higher odds of the ischemic event. Conversely, the Q4 was not significantly associated with the hemorrhagic outcome. It was observed that the ICH likelihood increases with DOAC plasma level raising. The relatively limited sample size may have reduced the statistical power to detect modest associations and interaction effects, potentially leading to the lack of statistically significant differences despite observable trends. The numerical difference between brain ischemic and hemorrhagic events in the analyzed cohort may have influenced the reduced predictive power of DOAC plasma levels to accurately predicting ICH.

Conclusions. Low DOAC plasma concentrations consistently emerged as the strongest predictor of brain thromboembolic events. The ICH likelihood increases with DOAC plasma level raising. The results of this study should be interpreted as hypothesis-generating. Larger prospective studies with standardized pharmacokinetic assessment will be required to better define the relationship between DOACs exposure and cerebrovascular outcomes.

