Study project version 2, 16-04-2023

Title

Thromboembolic and BLEEding events while on direct oral anticoagulant treatment: role of DOAC tests in the Emergency Department. The T-BLEEDOAC study.

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Synopsis

Background	Oral anticoagulation (OAC) reduces the risks of ischemic stroke (IS) and systemic embolism (SE) in patients affected by atrial fibrillation (AF) by 60-70%. The management of patients presenting an acute IS or SE despite OAC treatment remains challenging for clinicians, as current evidence on factors leading to the failure of OAC is still not definite. Risk of recurrent venous thromboembolism (VTE) is usually low while on anticoagulant treatment (nearly 2%), but in some patients as in those with active cancer it can exceed 8% per year. Major international guidelines do not give strong recommendations on the management of thrombotic events while on OAC treatment. Similarly, in patients with major bleeding (MB) while on OAC treatment, management is challenging. Vitamin K-antagonists (VKA) action can be easily detected by the international standardized ratio (INR) and the management of patients experiencing events while on AVK is usually based on INR values. Regarding direct oral anticoagulant (DOAC) plasma levels there is no consensus on the recommended cut-off to rule out an anticoagulant effect. Moreover, its determination requires experienced personnel which may not be available 24 hours a day and in small hospitals. Quick, accessible and accurate point-of-care (POC) tests are needed for detecting DOAC activity in emergency situations. Recently, a qualitative test to detect the presence of DOACs in human urine has been developed. This test may help physicians in decision making, but evidence on its use in emergency situations is limited.
Population	Patients receiving DOACs at therapeutic doses for atrial fibrillation or venous thromboembolism experiencing a thrombotic or bleeding event.
Study Objectives	The primary study objective is to assess the correlation between DOAC plasma level at admission and urine DOAC Dipstick result (positive or negative for the presence of DOAC). The secondary objectives are to assess predictors of in-hospital all-cause death, disability, clinical hemodynamic or neurological or neuroradiological worsening, number of red blood cells (RBC) transfusion, need to administer reversal therapy.
Incusion criteria	Patients could be included if: 1) age ≥18 years; 2) ongoing treatment with DOAC at therapeutic doses (at least 7 days from start); 3) admitted to the hospital for an IS/SE/recurrent VTE/MB; 4) provided informed consent.
Exclusion criteria	Traumatic events

Study design	Prospective cohort study on adult patients receiving therapeutic doses of DOACs and admitted to the ED for acute thromboembolic event (IS, SE, recurrent venous thromboembolism [VTE]) or for non-traumatic MB. The role of DOAC plasma levels and of DOAC Dipstick at hospital admission will be evaluated in these patients. At the time of admission for index IS/SE/recurrent VTE or MB, plasma samples for DOAC levels will be obtained from the samples collected as per routine practice and then locally processed and analyzed. As per local practice, urine samples will be obtained at the time of admission and on-site test will be performed to assess DOACs presence by DOAC Dipstick (DOASENSE GmbH, Heidelberg, Germany) and analyzed with DOASENSE Reader, provided on loan for use by "A.De Mori Strumenti" S.p.A. Clinicians will be free to decide on the IS/SE/recurrent VTE/MB treatment and to change or not the anticoagulant treatment after the index event. In case of bleeding events, clinicians will be free to decide the management of the hemorrhagic complication, including reversal therapies when indicated. Patients will be followed up prospectively until hospital discharge. Outcome adjudication will be performed by in a blinded fashion by an independent physician.
Study duration	1 year
Study design	Multicenter prospective study
Number of patients to be included	40 patients will be included at each study center
Outcome	The primary study objective is the correlation between DOAC plasma level at admission and urine DOAC Dipstick result (positive or negative for the presence of DOAC). Secondary outcomes are: i) the composite of in-hospital all-cause death or disability (modified Rankin Scale >2); ii) in-hospital death in the overall population and according to index event; iii) disability at discharge in patients with IS or intracranial haemorrhage; iv) death due to PE or early hemodynamic instability in patients with recurrent VTE; v) fatal bleeding or early hemorrhagic shock in patients with MB; vi) clinical or neuroradiological worsening in patients with cerebral thrombotic or hemorrhagic event; vii) number of red blood cells (RBC) transfusion and/or the need to administer reversal therapy.

Statistical analysis	The correlation between DOAC plasma level at admission and urine DOAC Dipstick result will be assessed. Receiver Operating Characteristic (ROC) curves will be derived for different DOAC plasma levels cut-off (<50, 50-100, >100ng/ml, and <30, ≥30 ng/ml). A univariate analysis will determine the strength of association between: i) each potential predictor and primary study outcome; ii) each potential predictor and all-cause death; and iii) each potential predictor and disability. Predictors resulting associated with study outcome at univariate analysis will be combined in a multivariate fashion. All associations will be presented as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs), p-value. Study outcome events will be presented as the total number of first events.
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