Acute Stroke Treatment in Patients Receiving Direct Oral Anticoagulants: Is it Time to Review the Guidelines?

Owing to their favorable safety profile, a substantial number of patients are nowadays being prescribed direct oral anticoagulants (DOACs), for either atrial fibrillation, venous or pulmonary thrombosis, etc.[1,2] In the event of an acute ischemic stroke in these patients, there is a dilemma about the use of acute stroke treatments, namely, intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT). The current European and American acute stroke treatment guidelines recommend withholding IVT for patients who have used DOACs within 48 hours of presentation unless laboratory tests suggest subtherapeutic anticoagulation.[3,4] The justification being a high presumed risk of haemorrhagic complications but the data supporting this recommendation is limited and heterogeneous.[5]

The 2019 American Heart Association and American Stroke Association (AHA-ASA) acute stroke guidelines[4] suggest IVT alteplase should not be administered to these patients unless appropriate laboratory tests, such as activated partial thromboplastin time (aPTT), International normalized ratio (INR), platelet count, ecarin clotting time, thrombin time, or direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for more than 48 hours (assuming normal renal metabolizing function). There was never an explicit negative recommendation for EVT in patients who had taken DOACs within the last <48 hours.[6]

The current study, a systematic review and meta-analysis, analyzed the evidence for safety and efficacy of recanalization therapy in acute ischemic stroke (AIS) patients who were receiving DOAC therapy.[7] They wanted to improve upon the limitations of a prior meta-analysis published in the year 2020, which had included only nine studies.[8] The current study included 17 studies (14 for EVT; 3 for IVT) published till March 2021. It found a lower risk of symptomatic intracranial haemorrhage (sICH) in patients on DOACs undergoing EVT compared to those not anticoagulation therapy (RR = 0.85, 95% CI = 0.72 to 1.00, $P = 0.04$). However, DOACs were noted to be associated with poorer functional recovery at three months, quite likely due to older age and more frequent comorbidities of the anticoagulation group.[7] Both AHA-ASA and European Stroke Organization (ESO) guidelines mention EVT being safe in this subset of patients and the current study also reiterates that.[3] Regarding the safety of IVT in AIS patients on DOAC therapy, there were no significant differences in sICH rates (RR = 0.87, 95% CI = 0.48 to 1.58, $P = 0.64$).

The current study is a well-conducted one and has tried to address an important clinical question. The findings might prompt revision of current guidelines or initiation of further studies. An important limitation of the study is that only three studies on IVT were published till the year 2017 and one out of them that accounted for nearly half of the patients is a retrospective study. This compromises the strength of evidence on the safety of IVT. In the meantime, another meta-analysis was published elsewhere.[9] The current study is not able to resolve some key clinical questions:

Q1: Should one use specific or non-specific clotting tests to assess the level of anticoagulation with DOACs prior to administration of IVT? Current guidelines suggest IVT for patients consuming DOACs in the last 48 hours prior to AIS, only if appropriate laboratory tests, such as aPTT, INR, platelet count, ecarin clotting time, thrombin time (<60 sec), or direct factor Xa activity assays are normal (<0.5U/ml). Therefore, patients on DOACs could safely undergo IVT if DOAC dosing is found subtherapeutic on performing specific clotting tests.[3,4]

Q2: What is the evidence on the safety and efficacy of a reversal agent for DOACs? Eight out of nine expert members of the group writing ESO guidelines suggest using the combination of idarucizumab prior to IVT with alteplase. This consensus was based on the safety data from two national cohorts of Germany and New Zealand.[10,11] However, there is a need for conducting randomized control trials exploring this subject. With regards to reversal of factor Xa inhibitors, andexanet alfa has not been approved as yet, as the infusion itself takes about two hours to administer, using up valuable time. Its cost, efficacy, and availability are issues as well.[3] A retrospective study had shown thrombotic complications of 16.7% with its use.[12]

Q3: Is there any data on IVT in AIS patients on DOAC irrespective of the results of clotting tests or the use of reversal agents? A recent study published by Meinel *et al*.[9] in 2023 has alluded to this issue. It is a retrospective analysis of patient data from 64 centers, which included 832 patients with recent DOAC ingestion and 32,375 control patients who had received IVT without prior anticoagulation treatment. The primary outcome of unadjusted rate for sICH was 2.5% in the DOAC group and 4.1% in the control group, with an adjusted odds ratio of 0.57. Comparable sICH rates were observed with different selection strategies for thrombolysis: 1st: 3.1% among patients with DOAC level measurement, 2nd: 1.2% among patients with DOAC reversal with idarucizumab, and 3rd: 3.1% among those with neither DOAC level measurement nor reversal. Though that study had some limitations, it provides much-needed data for decision-making in real-life situations. If replicated, it could change the current practice of performing clotting tests or using a reversal agent prior to IVT.

To conclude, EVT could be safely considered in AIS patients with consumption of DOAC within the last 48 hours. Intravenous thrombolysis could be considered only after

ensuring a subtherapeutic anticoagulation by performing DOAC levels or specific laboratory tests. Those receiving dabigatran in therapeutic dose could be administered IVT after reversal with idarucizumab. More good-quality studies need to be done to solve the clinical dilemma regarding the use of IVT in patients on DOACs. A need to review the current guidelines may arise in the future.

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