Editorial Commentary | Palliative Medicine and Palliative Care for Other Serious or Advanced Diseases

Early start of anticoagulation in stroke—timing is essential!

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Current recommendations regarding anticoagulation and stroke in patients with atrial fibrillation (AF)

The start of therapeutic anticoagulation following stroke in patients with AF is an important question as a late onset might increase the risk of complications like recurrent ischemic stroke in patients (1,2). In patients with acute ischemic stroke and AF, early start of anticoagulation is associated with less recurrent stroke but with the risk of hemorrhagic transformation of the infarcted area (3). In the literature a later onset of 12 days is described in patients with hemorrhagic transformation following ischemic stroke in AF patients (3). The current guidelines recommend a start of therapeutic anticoagulation in the time frame of 7 to 14 days following the stroke (1,2). Early initiation of anticoagulation is not without reported risk, as one study showed that patients started on direct oral anticoagulants (DOACs) within 2 days of acute stroke had a composite rate of recurrence and major bleeding of 12.4%, and composite rates were 2.1% for those started on DOACs between 3 and 14 days, 9.1% for those started on DOACs >14 days after acute stroke (4). Thus, it still remains to elucidate when the best time to initiate treatment in patients with acute stroke is directly following the event or at different time in the first 4 days. However, these data have limitations as the study was observational and further patients were allowed to receive low molecular weight heparin before DOAC. In addition, the study had multiple selection bias to only include patients which were deemed at a low risk for hemorrhage or with mild stroke regarding impairment or small size (5).

Grading stroke severity in the context of functional impairment and imaging-based grading

The most often variable to grade stroke severity is the National Institutes of Health Stroke Scale (NIHSS) which increases due to the documented impairment with an increase of the score (6,7). In the recent years investigators did collect data of magnetic resonance imaging (MRI) in a multicenter approach to predict infarct size and location as the implications are important for decision-making and to establish prognosis in patients with acute stroke (8,9). As of current due to progressive establishment of neural networks in research and science prediction of the final infarct size can be established with the baseline MRI (8,9).

New evidence to start anticoagulation early following stroke associated with AF ELAN, OPTIMAS and TIMING trials

In the context of this background multiple studies are

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currently prospectively investigating if an early start of therapeutic anticoagulation might be non-inferior to the recommended approach with OPTIMAS and the completed ELAN and TIMING studies (10-12). In general, DOACs should be preferred, if possible, in patients with AF (13,14). Recent data from the large, randomised, international ELAN trial showed that early treatment was associated with an estimated 2.8% points lower and 0.5% points higher incidence of the composite of stroke, systemic embolism, bleeding or death at 30 days compared with later treatment (11). The approach to defining treatment initiation in this trial was based on imaging with the following definitions: an infarct of 1.5 cm or less was defined as small; an infarct in the distribution of a cortical superficial branch of the middle, anterior or posterior cerebral artery was defined as moderate; and larger infarcts in the distribution of these arteries or a brainstem or cerebellar infarct larger than 1.5 cm were defined as large (11). According to this imaging-based definition of stroke size the anticoagulation was started in the ELAN study in the first 48 hours in minor and moderate stroke and on day 6 to 7 in a major stroke (11). The treatment approach with early start of DOAC treatment in the first 48 hours in case of minor or moderate stroke is differing from similar designed studies (10,12) and could be an important approach to individualize the treatment in patients. In comparison to the imaging-based scheme in ELAN the TIMING study did randomize the patient in the first 72 hours with an allocation to early start of DOACs with ≤4 days or a delayed start with ≥5 to 10 days (12). The still ongoing OPTIMAS study which investigates if start of DOACs within 4 days of stroke onset is as effective or better than delayed initiation 7 to 14 days from the onset event did not report the outcomes yet (10). Thus, the time to start anticoagulation is still different in ELAN which did us an imaging-based approach to start anticoagulation in comparison to TIMING and OPTIMAS (10-12).

Reported risk and adverse events in ELAN, TIMING and the current literature

It still remains to be elucidated when the best time to initiate treatment in patients with acute stroke is, directly following the event or at different time in the first 4 days. Thus, the approach the investigators did decide in the multicenter ELAN study (11) is very important and has implications regarding adding new diagnostic features to the current algorithms regarding the treatment of stroke. In the studies presented, the researchers (11) used an imaging-based definition of stroke severity because the alternative, the NIHSS score, depends on both the location and size of the infarct. Several studies have linked infarct size, measured by volume analysis or semiquantitative measures, to the risk of hemorrhagic transformation (4). However, in contrast the data published previously in an observational trial (4) the results of ELAN suggest that the incidence of symptomatic intracranial hemorrhage is low with 2 patients (0.2%) each in the early and late treatment arm at 30 and 90 days (11) and in TIMING even no cases of intracranial hemorrhage were reported (12). The TIMING study with a similar design in which the hypothesis of non-inferiority regarding the early start of anticoagulation (12) was investigated the patients were randomized in the first 4 days to anticoagulation but not as described in the featured study (11) within the first 48 hours. The study could show that the early initiation of DOACs was noninferior to a delayed start (>4 days) after acute ischemic stroke in patients with AF (12). The authors concluded from their data that due to the lower rates of ischemic stroke and death and the absence of symptomatic intracerebral hemorrhages the early start of DOACs was safe and should be considered for acute secondary stroke prevention in patients eligible for DOAC treatment (12). Although both studies could show that the early start of anticoagulation is safe and seems to be non-inferior to the current guideline-based approach still the optimal risk prediction regarding the residual risk of causing harm due to hemorrhagic transformation of stroke as reported (4) needs to be defined in this setting. The featured study and additional research using an imaging-based classification seems to be very reliable regarding this risk assessment (8,9,11).

Summary of the ELAN study

In summary, the ELAN study underlines that an early start of DOAC treatment in acute ischemic stroke and AF is feasible and associated to a low risk, even when the treatment is started in the first 48 hours following the acute event. The essential and needed risk stratification was done with an imaging-based risk assessment which differentiated between minor and moderate stroke, eligible for treatment in the first 48 hours and major stroke with treatment start at day 6 or 7 following the event. Additional data are however still needed to show the feasibility of this approach and if a

modification of the guidelines should be evaluated.

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