Message From the Editor-in-Chief | Palliative Medicine and Palliative Care for Serious or Advanced Diseases

The optimal timing of oral anticoagulation therapy for ischemic stroke management

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The January 2024 issues of *Annals of Palliative Medicine* featured 6 Editorials, 8 Original Articles, 6 Review Articles, 2 Case Reports, 3 Editorial Commentary Articles, and 3 Letters to the Editor.

One of the Editorial Commentaries (1), written by Christoph Sinning of the Department of Cardiology, University Heart & Vascular Center Hamburg, Hamburg, Germany and the German Centre of Cardiovascular Research, Partner Site Hamburg/Kiel/Lübeck, Hamburg/Kiel/Lübeck, Germany, will be featured in this Message From the Editor-in-Chief. That Editorial Commentary discusses the highly impactful Early versus Late Initiation of Direct Oral Anticoagulants in Post-ischemic Stroke Patients with Atrial Fibrillation (ELAN) randomized trial assessing the timing of direct oral anticoagulation therapy in patients with atrial fibrillation following an ischemic stroke that was recently published in the *New England Journal of Medicine* (2).

Stroke is the second-leading cause of death and third-leading cause of combined death and disability worldwide. Furthermore, since 1990, there has been a 70% increase in incident strokes and 43% increase in deaths from strokes (3). Unfortunately, projections indicated that the incidence rate of ischemic stroke will increase further worldwide across both sexes, all age groups, and all socio-demographic index quintiles over the next decade (4).

In addition to stroke being a leading cause of death, its morbidity and impact on patient quality of life is profound, with approximately half of all stroke survivors being chronically disabled (5,6). In developed countries, as up to 85% of stroke victims now survive, there is an increasing emphasis on preventing additional strokes and morbidity in these patients surviving their first ischemic event (6). The risk of a subsequent stroke after an initial stroke is approximately 5% per year, with the risk being higher in the first few weeks and months after the initial event (7).

Direct oral anticoagulants have been shown to reduce the risk of ischemic stroke and systemic embolism in patients with atrial fibrillation (8). It is less clear, however, if the timing of such anticoagulation initiation impacts the risks of stroke recurrence and bleeding in patients who suffered from an acute ischemic stroke. Early initiation of anticoagulation can increase the risk of intracranial hemorrhage in this patient population, favoring a delayed anticoagulation administration approach. However, later initiation can increase the risk of early ischemic event recurrence, favoring an early administration approach (2,8).

With limited randomized data guiding the timing decision, current guideline recommendations vary. While many guidelines recommend delayed administration, some guidelines recommend earlier administration of anticoagulation for more minor ischemic events relative to major ischemic strokes since the risk of hemorrhage has been reported to correlate with infarct size (9).

The ELAN trial, funded by the Swiss National Science Foundation and others, was an investigator-initiated, open-label trial enrolling patients from 103 sites across 15 countries. Participants were randomized to receive early anticoagulation, defined as being within 48 hours after a minor or moderate stroke or being on days 6 or 7 after a major stroke, versus later anticoagulation, defined as being on days 3 or 4 after a minor stroke, days 6 or 7 after a moderate stroke, or days 12, 13, or 14 after a major stroke. The primary outcome measure was a composite of recurrent ischemic stroke, systemic embolism, major extracranial

bleeding, symptomatic intracranial hemorrhage, or vascular death occurring within 30 days after randomization, with assessors blinded to the study arm assignments. Secondary endpoints included the components of the composite primary outcome at 30 days and at 90 days (2).

The study randomized 2,013 patients, of whom 37% had a minor stroke, 40% had a moderate stroke, and 23% had a major stroke. By 30 days, 29 patients (2.9%) suffered a primary-outcome event (2.9%) in the early-treatment group, whereas 41 patients (4.1%) suffered such an event in the later-treatment group [95% confidence interval (CI): −2.84 to 0.47]. Recurrent stroke was nearly twice as likely in the later-treatment group at both 30 days (2.5% *vs.* 1.4%, odds ratio, 0.57; 95% CI: 0.29 to 1.07) and 90 days (3.1% *vs.* 1.9%, odds ratio, 0.60; 95% CI: 0.33 to 1.06), but these differences were not statistically significantly. Two cases of symptomatic intracranial hemorrhage occurred in each arm (0.2%) by 30 days. Serious adverse events by 90 days occurred in 13.9% of patients in the early-treatment arm and 15.8% in the later-treatment arm. The ELAN authors concluded that early treatment initiation can be supported if indicated or if desired (2).

These findings are not dissimilar from a 2022 systematic review and meta-analysis of randomized-controlled clinical trials and prospective observational studies assessing ischemic stroke recurrence, all-cause mortality, symptomatic intracerebral hemorrhage, and any intracerebral hemorrhage following early (within 1 week) versus late (within 2 weeks) initiation of anticoagulation in patients with acute ischemic stroke due to atrial fibrillation in 5,616 patients (10). Patients that received anticoagulants within the first week after an acute ischemic stroke had similar rates of recurrent ischemic stroke, symptomatic intracerebral hemorrhage, and all-cause mortality compared to patients receiving anticoagulation within 2 weeks, with the study concluding that early anticoagulation initiation has similar efficacy and safety relative to later anticoagulation.

In the Editorial Commentary in *Annals of Palliative Medicine* (1), Sinning should be commended for doing a terrific job of putting the ELAN trial in the context of current recommendations regarding anticoagulation and stroke in patients with atrial fibrillation. He also discusses current approaches to grading stroke severity, which was the primary determinant of timing of anticoagulation in the ELAN trial. Sinning then provides details of and data from other trials investigating the timing of anticoagulation following stroke, including the OPTIMAS (11) and TIMING (12) trials, as well as the risks and adverse events reported across trials and the current literature based on anticoagulation timing.

The Editorial Commentary concludes that the ELAN study demonstrated that an early start of direct oral anticoagulants for acute ischemic stroke in patients with atrial fibrillation is feasible and associated with a low risk of adverse events, but that additional data are needed to prove the feasibility of this approach and if current guidelines should be reevaluated.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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