Teaching Course 9

New insights in the management of patients with ischaemic stroke or TIA - Level 2

Secondary prevention after stroke and atrial fibrillation

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Introduction

Patients with acute cardioembolic stroke and atrial fibrillation (AF) are at a high risk of early recurrence and anticoagulants are known to be the most effective secondary stroke prevention therapy (Arnao et al, 2015). The starting timing of this therapy is controversial.

In this teaching course, the following scenarios will be analysed:

1.) Risks of recurring thromboembolic events in acute stroke and AF
2.) Risks of haemorrhagic transformation events in acute stroke and AF
3) Early anticoagulation and its associated risks of thromboembolic events or
   intra-cerebral bleedings
3.1) Early anticoagulation with LMWH and Vitamin K Antagonist
3.2) Early anticoagulation with DOACs
4.) Future Directions
1.) Risks of recurring thromboembolic events in acute stroke and AF

In patients with cardioembolic stroke associated with AF, the risk of early stroke recurrence, defined as a new event occurring within 2 weeks, has been reported to range between 0.1% and 1.3% per day (Hart et al, 1983; Kelley et al, 1984). Within 48 hours from stroke onset in patients with AF, the risk of recurrent stroke in the International Stroke Trial was reported to be 4.8% (Saxena et al, 2001). Within 90 days, overall, this risk, and the risks of transient ischemic attack (TIA) and systemic embolism was reported to be 7.6%. Another recent study has reported old age, large lesion size and atrial enlargement to be predictive factors for ischemic outcome events (Paciaroni et al, 2015; Yaghi et al, 2015).

2.) Risk of haemorrhagic transformation in patients with acute stroke and AF

In patients with acute stroke, the early risk of haemorrhagic transformation was reported to be about 9% and cardio embolism resulted in being an independent risk factor for Parenchymal Hematoma (PH) which was correlated with bad outcome, defined as a combination of mortality and disability (Paciaroni et al, 2008). In this study, at day 7 day from stroke onset, of 300 patients with cardioembolic acute stroke, 7% had a haemorrhagic transformation type PH. In the RAF study, between 48 hours from stroke onset and 90 days, the risk of symptomatic haemorrhagic transformation was about 4% and in these patients. Whereas, large lesion size was an independent risk factor for symptomatic intra-cerebral bleeding (Paciaroni et al, 2015). Small lesions were associated with low rates of symptomatic cerebral bleeding, as well as stroke recurrence.
(Paciaroni et al, 2015). These small lesions, when subcortical, is often due to untreated small vessel disease which carries a lower risk of recurrence, compared to cardioembolic lesions.

3) Early anticoagulation and its associated risks of thromboembolic events or intra-cerebral bleedings

To date, RCTs have failed to produce any evidence supporting the administration of heparin in patients with acute ischemic stroke within 48 hours from stroke onset (Gubitz et al, 2004; Beri at al, 2008; Whiteley et al, 2013). A meta-analysis involving 4,624 patients with acute cardioembolic stroke, mainly with AF, suggested that early anticoagulation was associated with a non-significant reduction in recurrence of ischemic stroke, no substantial reduction in death and disability, and an increased intracranial bleeding (Paciaroni et al, 2007, Micheli et al, 2008). Abdul-Rahim et al (2014), suggested that the introduction of anticoagulants at 2-3 days post-stroke, so to achieve a therapeutic anticoagulation level by days 5-7, when Vitamin K antagonist was used; was associated with substantially fewer recurrent stroke events over the following weeks but with no excess risk of symptomatic intra-cerebral haemorrhages. Likewise, Palm et al., (2014) reported that early treatment (during hospitalization) with anticoagulants reduced mortality. The RAF study reported that in patients with acute stroke and AF, the optimal time for initiating anticoagulation treatment as secondary stroke prevention, was 4 to 14 days from stroke onset; at day 4 INR≥2 when the traditional Vitamin K antagonist was used. (Paciaroni et al., 2015)
3.1) Early anticoagulation with LMWH and Vitamin K Antagonist

In the RAF study, 14.7% of the patients received low molecular weight heparin (LMWH) alone, 37.8% vitamin K antagonists, 12.1% direct oral anticoagulants, and 36.0% LMWH followed by vitamin K antagonists (bridging therapy). Patients treated with oral anticoagulants alone had a better outcome compared to those treated with either LMWH followed by oral anticoagulants or with LMWH alone. About 7% of the patients treated with oral anticoagulants alone had an outcome event compared to 16.8% and 12.3% of those treated with LMWHs alone or followed by oral anticoagulants, respectively (p=0.003). These latter two results could have been influenced by the fact that these patients were shown to have higher risks of symptomatic intracranial bleeding, when the treatment was started 48-72 h from index event. However, it cannot be excluded that the small-lesion patient group might have been selected for oral anticoagulant strategy while the those who had received bridging therapy might have been more severe patients. Hallewi et al reported patients with acute stroke and AF, heparin or enoxaparin bridging increased the risk for serious bleeding (Hallevi et al, 2008).

3.2) Early Anticoagulation with DOACs

Only 20.1% of DOAC-treated patients in RE-LY (Connolly et al.,2009) and 18.6% of DOAC treated patients in ARISTOTLE (Granger CB, 2011) were reported to have a history of previous TIA or ischemic stroke. In ENGAGE AF-TIMI 48 (Giugliano et al., 2013) 28.3% of the DOAC-treated patients had a history of cerebrovascular ischemic event. Patients included in ROCKET AF (Patel et al., 2011) had, in comparison to patients of the other randomized DOAC trials, higher CHADS2 -scores. Moreover, 52.6% of the DOAC-treated patients had a history of previous TIA or ischemic stroke.
However, a subgroup-analysis of these latter patients were similar to those reported for full cohorts in all randomized trials (Hankey et al., 2012).

To date, no major randomised trial on DOACs, has investigated for their efficacy and safety in early secondary prevention. Specifically, in ARISTOTLE (Granger et al., 2011) all patients were randomised after day 7 post stroke, while in both RE-LY and ROCKET, AF patients were done so after day 15. Severe and disabling stroke patients in RE-LY () were precluded until after 180 days from onset, and in ROCKET AF (Patel et al., 2011) this was done for until after 90 days. Moreover, TIA patients could be included in ROCKET AF only following day 3-day post TIA. The ENGAGE AF-TIMI 48 trial (Giugliano et al., 2013) precluded patients with any ischemic stroke type up until day 30.

There are prospective data available on the safety and efficacy of early secondary prevention using DOACs subsequent to cardioembolic stroke from observational studies. Of these, the SAMURAI-NVAF study reported that no ICH was recorded after a DOAC-initiation within a median of four days post stroke. (Toyoda et al., 2015). Whereas, another observational study reported no significant difference in the rate of recurrent ischemic events when comparing delivery within 7 days and after 7 days (p=0.53).

The recently published prospective observational multicentre RAF-DOAC Study compared the rates of early recurrence and major bleeding (within 90 days) with the times of DOAC initiation in patients with acute ischemic stroke and atrial fibrillation. In this study, 381 patients (33.8%) were treated with dabigatran, 366 (32.5%) with rivaroxaban, and 380 (33.7%) with apixaban. Thirty-two patients (2.8%) had early recurrence, and 27 (2.4%) had major bleeding. The rates of early recurrence and major bleeding were, respectively, 1.8% and 0.5% in patients receiving
dabigatran, 1.6% and 2.5% in those receiving rivaroxaban, and 4.0% and 2.9% in those receiving apixaban. Patients who initiated DOACs within 2 days after acute stroke had a composite rate of recurrence and major bleeding of 12.4%; composite rates were 2.1% for those who initiated DOACs between days 3 and 14 and 9.1% for those who initiated >14 days after acute stroke. In patients with acute ischemic stroke and atrial fibrillation, treatment with DOACs was associated with a combined 5% rate of ischemic embolic recurrence and severe bleeding within 90 days. (Paciaroni et al., 2017). Based on these results, the American Stroke Guidelines recommend that “for most patients with an acute ischemic stroke in the setting of atrial fibrillation, it is reasonable to initiate oral anticoagulation within 4 to 14 days after the onset of neurological symptoms.” (Class of Evidence, II a and Level of Evidence B (based on non-randomised studies). (Powers et al., 2018)

4) Future Directions:
Currently, RCTs are investigating the time of initiating DOACs in acute cardioembolic stroke patients. Of these, the “Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke with Atrial Fibrillation” study will compare early and late initiation of DOACs in adult patients with both acute ischemic stroke and atrial fibrillation. This is an ongoing registry-based randomised clinical trial (R-RCT) using The Swedish Stroke Register (Riksstroke). Half of the patients will start DOACs early: within 4 days after stroke onset. While the remaining will start late: 5-10 days after stroke onset. While the remaining will start late: 5-10 days after stroke onset. https://clinicaltrials.gov/ct2/show/NCT02961348.
The “Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischaemic Stroke Patients with Atrial fibrillation study (ELAN) is an ongoing international, multicentre, randomised-controlled, two-arm,
assessor-blinded trial that aims to estimate the net benefit of early versus late initiation of DOACs in patients with acute ischaemic stroke related to AF. https://clinicaltrials.gov/ct2/show/NCT03148457. Both of the aforementioned trials are scheduled to conclude their randomisations by 2021. Their results will influence the direction of international recommendations and guidelines regarding the optimal timing for initiating anticoagulation for cardioembolic stroke patients with AF.
References


