Immediate Anticoagulation for Acute Stroke in Atrial Fibrillation

Yes

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Meta-analyses contest the value of “immediate” anticoagulation in acute stroke although the trials included in these analyses referred to patients treated protractedely and the anticoagulants examined had significant pharmacological differences. Post hoc analyses of some of these trials extend the overall negative effects of anticoagulation to patients with stroke secondary to atrial fibrillation (AF). The value of immediate anticoagulation in patients with acute stroke secondary to AF, alike its role in any other stroke subtype, has not been adequately explored. Thus, I agree that “delayed” anticoagulation is not beneficial for stroke attributable to AF, although I defend that to bring down the value of “immediate” anticoagulation is premature. Absence of evidence is not equal to evidence of absence.

Observational data suggest that full anticoagulation with unfractionated heparin (UH) started within <6 hours from clinical onset is better than delayed anticoagulation. The Rapid Anticoagulation Prevents Ischemic Damage (RAPID) trial is the closest randomized approach to immediate anticoagulation, with a mean treatment delay of 6.9 hours. Other trials delayed treatment for 24 (Trial of Org 10172 in Acute Stroke Treatment [TOAST], Fraxiparin in Stroke Study Bis [FISS bis]), 30 (Heparin in Acute Embolic Stroke Trial [HAEST]) or 48 hours (FISS, Tinzaparin in Acute Ischemic Stroke Trial [TAIST], International Stroke Trial [IST]), and some of them are also limited by unblinding of treatment, ill-timed use of CT, or ambiguous definitions of end points (ie, recurrent stroke). The RAPID trial confirmed the higher risk of bleeding by excessive anticoagulation. Therefore, the omission of monitoring of biological effects is especially worrisome in previous UH trials. Endocrinologists might have also suspected the safety of insulin if the agent had been explored in trials ignoring serum glucose levels.

RAPID was an academic effort to reconcile science and simplicity, but insufficient funding dissuaded many investigators to participate. The main rationale of the study implied that UH is an anticoagulant with time-dependent anti-inflammatory properties. Unfortunately, a hopeless recruitment rate led to the premature termination of the study when only 67 patients had been included. Nevertheless, RAPID was able to show a trend toward more effective prevention of stroke recurrence with UH (0%) than aspirin (8.6%; \( P=0.09 \)) and without an increment in serious bleeding (8.6% for aspirin, 6.3% for UH; \( P=0.71 \)).

Delaying anticoagulation in stroke secondary to AF was advocated in the late 80s for the fear of facilitating early hemorrhagic transformation. However, since the mid 90s we know that carefully monitored UH is safe, even in patients with large infarcts attributable to AF. But the urgency of full anticoagulation is mainly justified in light of the molecular mechanisms of brain ischemia. Predictably, during the crucial hours that went before patients reached adequate anticoagulation in previous trials, excitatory amino acids, cytokines, calcium, and free radicals peaked to high levels that dwindled the extent of salvageable brain tissue. Treatment delay for 1 or 2 days is trivial if our primary aim is to decrease the risk of early stroke recurrence (HASTE trial). However, treatment delay may be of vital relevance if we aim primarily to improve functional outcome and reduce mortality (as did all other anticoagulation trials). Only an (unrealistic) extremely large reduction of recurrent strokes would translate into improved functional outcome at follow-up. But this approach is early secondary stroke prevention rather than acute stroke therapy.

Stroke secondary to AF has triggered special concerns because it was thought to represent a situation of higher risk of early stroke recurrence although more recent information opposes this concept. Then, a more liberal anticoagulation attitude for the fear of early recurrence is unwarranted. Rather, the central issue that calls for a serious testing of immediate anticoagulation in stroke secondary to AF is what I would define as the tissue factor (TF) link. Briefly, TF follows the release of cytokines after stroke and is the primary cellular initiator of the coagulation cascade in vivo. TF behaves as a hemostatic envelope diffusely expressed in the adventitia of cerebral vessels, but there is also prominent TF expression in the human cortex. Accordingly, any acute embolic stroke, including that secondary...
to AF, is a TF-mediated prothrombotic state that could theoretically be opposed with adequate anticoagulation. Therefore, the TF link emphasizes the consequences rather than the causes of stroke for treatment decisions. Given that UH achieves faster anticoagulation levels than any other regimen, I recommend this therapy for many of my patients if there are not contraindications. Calibration of activated partial thromboplastin time ratios to their corresponding heparin levels (0.3 to 0.5 U/mL), careful monitoring, and frequent dose adjustments are essential safety measures. However, I strongly believe that Peter Sandercock, my contestant in this controversy and good friend in less controversial issues, shares with me that a well-funded RAPID II trial is urgently needed.

Disclosures
None.

References

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