Neurofilament light chain (NFL) - a neuron-specific plasma biomarker for evaluating risk of ischemic cerebral events in atrial fibrillation

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Background: A history of ischemic stroke is one of the strongest risk factors for future stroke in patients with atrial fibrillation (AF). Circulating biomarkers specific for the brain may be used to detect overt and covert cerebral ischemia. Neurofilament light chain (NFL) is a neuron-specific cytoskeleton protein that is released into blood at increased levels when the brain is injured and may be a complement to already established risk factors of AF.

Purpose: We hypothesized that NFL measured in plasma (pNFL) is an independent and incremental risk indicator of ischemic stroke in patients with AF.

Methods: pNFL was measured in venous blood samples from 1,056 patients with AF randomised to aspirin in the ACTIVE A trial. Samples were collected at randomisation and the median follow-up duration was 3.6 years. pNFL was analysed with a single molecule array. Associations between pNFL and subsequent clinical outcomes were evaluated by Cox-regression models adjusted for fifteen clinical characteristics and NT-proBNP levels.

Results: The median concentration of pNFL was 17.3 (interquartile range 10.9-28.3) ng/L. The variables most strongly associated with higher pNFL levels were advanced age, renal dysfunction, lower body mass index, prior stroke/transient ischemic attack and female sex. In multivariable analyses, pNFL was a stronger risk indicator for ischemic stroke than any clinical factor, including previous stroke (Figure 2), and of similar prognostic importance as NT-proBNP. pNFL was independently associated with ischemic stroke (per doubling of pNFL, hazard ratio [HR] 1.23, 95% confidence interval [CI] 1.01-1.50, p=0.038), all-cause death (HR 1.30, 95% CI 1.12-1.51, p<0.001) and heart failure (HR 1.30, 95% CI 1.09-1.54, p=0.003) when adjusting for both clinical characteristics and other biomarkers including NT-proBNP. pNFL improved the discriminatory value (c-index) for ischemic stroke from 0.676 to 0.686 (p=0.038) when added to a fully adjusted model including NT-proBNP.

Conclusions: In patients with AF, pNFL was associated with an increased risk of ischemic stroke, independent of clinical characteristics and NT-proBNP. pNFL was a stronger risk factor for ischemic stroke than previous stroke and of similar prognostic importance as NT-proBNP. pNFL may be a novel plasma biomarker improving the evaluation of the risk of ischemic cerebral events in patients with AF.
Figure 1. Cumulative event rate of ischemic stroke by quartile groups of pNFL.

Stroke risk by pNFL quartile group
Figure 2. Variable importance within the fully adjusted model for the risk of ischemic stroke.