Serial measurement of biomarkers and the risk of stroke or systemic embolism and bleeding in patients with atrial fibrillation in ENGAGE AF-TIMI 48

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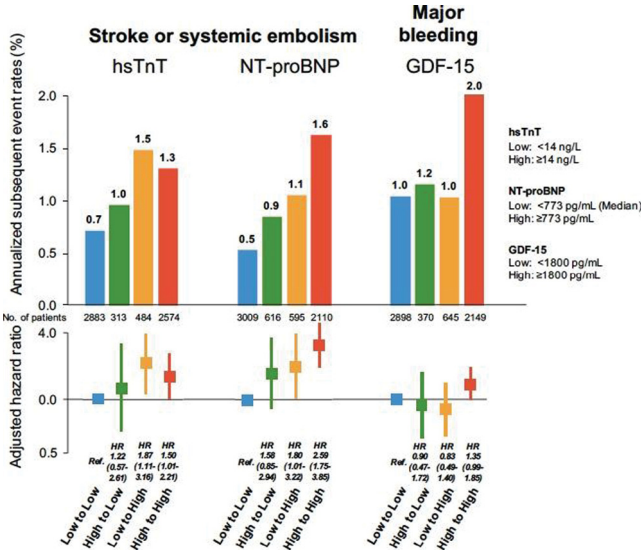
Funding Acknowledgement: Type of funding source: Private company. Main funding source(s): Daiichi Sankyo Pharma Development

Background: Patients with atrial fibrillation (AF) have progressive cardiac structural changes that may be manifest by biomarkers of myocardial injury and hemodynamic stress. Baseline values of hsTnT (high-sensitivity troponin T), and NT-proBNP (N-terminal pro-brain natriuretic peptide) are associated with stroke risk and GDF-15 (growth differentiation factor-15) is associated with bleeding risk in patients with AF. However, the variability of these biomarkers over time and their associations with stroke or systemic embolism events (S/SEE) and bleeding in patients with AF remain unclear.
Purpose: We examined whether patients with AF demonstrate detectable changes in these biomarkers over 12 months and whether such changes from baseline to 12 months are associated with the subsequent risk of S/SEE (hsTnT, NT-proBNP) and bleeding (GDF-15).
Methods: ENGAGE AF-TIMI 48 was a multinational randomized trial of the oral factor Xa inhibitor edoxaban in patients with atrial fibrillation and a CHADS2 score ≥2. We performed a nested prospective biomarker study in 6062 patients, analyzing hsTnT, NT-proBNP, and GDF-15 at baseline and 12 months. Event rates were estimated and displayed with annualized event rates after 12 months.
Results: Of 6062 patients, hsTnT was dynamic in 46.9% (≥2 ng/L change), NT-proBNP in 51.9% (≥200 pg/L change), GDF-15 in 45.6% (≥300 pg/L change) between baseline and 12 months. In addition, 7.7% in hsTnT shifted from low->high categories, 9.4% in NT-proBNP from low->high, 10.6% in GDF-15 from low->high over 12 months (Figure). Elevated hsTnT (≥14 ng/L) and NT-proBNP (≥900 pg/L) either at baseline or at 12 months were independently associated with higher rates of subsequent S/SEE, and elevated GDF-15 (≥1800 pg/L) either at baseline or at 12 months were independently associated with higher rates of subsequent bleeding (P<0.001 for each). In a Cox regression model, the absolute changes in log2-transformed hsTnT and NT-proBNP were associated with increased risk of S/SEE (adj-HR, 1.75; 95% CI, 1.38–2.23; p<0.001, and adj-HR, 1.31; 95% CI, 1.11–1.55; p=0.002, respectively) and log2-transformed GDF-15 with bleeding (adj-HR, 1.42; 95% CI, 1.04–1.92; p=0.025). Analyzed in a categorical manner (Figure), patients who increased hsTnT or NT-proBNP between baseline and 12 months or had high hsTnT or NT-proBNP at both timepoints were at higher risk for S/SEE (adj-HR 1.87 and 1.50 for hsTnT; adj-HR 1.80 and 2.59 for NT-proBNP, respectively). Patients with persistently elevated GDF-15 appeared to be at higher risk for bleeding (adj-HR,1.35) (Figure).
Conclusions: Serial assessment of hsTnT, NT-proBNP, and GDF-15 revealed a substantial proportion of patients with AF had dynamic values. Patients with either persistently elevated or dynamic values were at higher risk of adverse clinical outcomes. Those biomarkers may play a role in personalizing preventive strategies in patients with AF based on risk.



Change in biomarkers and event rate