# Atrial fibrillation and the prognostic performance of biomarkers in heart failure

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**Background:** Consideration of circulating biomarkers for risk stratification in heart failure (HF) is recommended in authoritative international guidelines but the influence of atrial fibrillation (AF) on the prognostic performance of many markers is unclear. Therefore we investigated the interactions between AF and biomarkers in prediction of important clinical outcomes in HF.

**Methods:** NT-proBNP, pro-atrial natriuretic peptide (MR-proANP), C-type natriuretic peptide (CNP), NT-proCNP, high-sensitivity troponin-T, high-sensitivity troponin-I, mid-regional-propeptide adrenomedullin (MR-proADM), co-peptin (PAVP), growth differentiation factor-15 (GDF-15), sST2, Galectin-3 and procalcitonin levels were measured in a prospectively designed, multicenter, longitudinal study of adults with HF. AF was defined as a documented history of AF based on medical records, and/or presence of AF/atrial flutter on baseline 12-lead ECG. The primary outcome considered was the composite of HF-hospitalization or all-cause mortality on prospective follow-up at 2-years. Cox proportional-hazards models were used in the prognostic evaluation of biomarkers, and each was tested for interaction with AF.

**Results:** Among 1,099 patients with HF (mean age 62±12 years, 28% female, mean left ventricular ejection fraction 35±16%), 261 (24%) patients had AF. Median levels of NT-proBNP, GDF-15, ST2, MR-proADM, proANP and CNP were higher in AF ($p<0.05$). Above-median levels of all 12 biomarkers were independently associated with increased risk of the primary outcome. Significant interactions with AF were detected for Galectin-3 and sST2. Galectin-3 (>7.7ng/mL) was associated with increased HF-hospitalizations (adjusted hazard ratio [AHR] 1.75, 95% C.I. 1.10–2.77) and all-cause mortality (AHR 1.95, 95% C.I. 1.04–3.63) only among patients with AF. The prognostic performance of sST2 (>35.6ng/mL) was also stronger in AF especially for the primary outcome (AF: AHR 2.06 95% C.I. 1.32–3.21; non-AF: AHR 1.49 95% C.I. 1.18–1.88) and HF-hospitalization (AF: AHR 1.65, 95% C.I. 1.01–2.69; non-AF: AHR 1.32, 95% C.I. 1.02–1.71). The association of Galectin-3 with the composite outcome was not modified by HF type (HFpEF vs HFrEF) (p for 3-way interaction=0.61) except for sST2 (p for 3-way interaction=0.018) where the association appeared stronger in patients with HFpEF and AF (HR 3.12, 95% C.I. 1.26–7.78) compared to those with HFrEF and AF (HR 1.83, 95% C.I. 1.01–3.33) although numbers of events in each subgroup were small. Notably, no such interactions were observed for the most frequently measured prognostic markers in HF including NT-proBNP and the high-sensitivity cardiac troponins.

**Conclusion:** AF modified the prognostic utility of guideline-endorsed HF-biomarkers, wherein prognostic associations of Galectin-3 and ST2 were limited to, or stronger in, patients with AF. Application of markers for prognostic purposes in HF requires consideration of the presence or absence of AF.

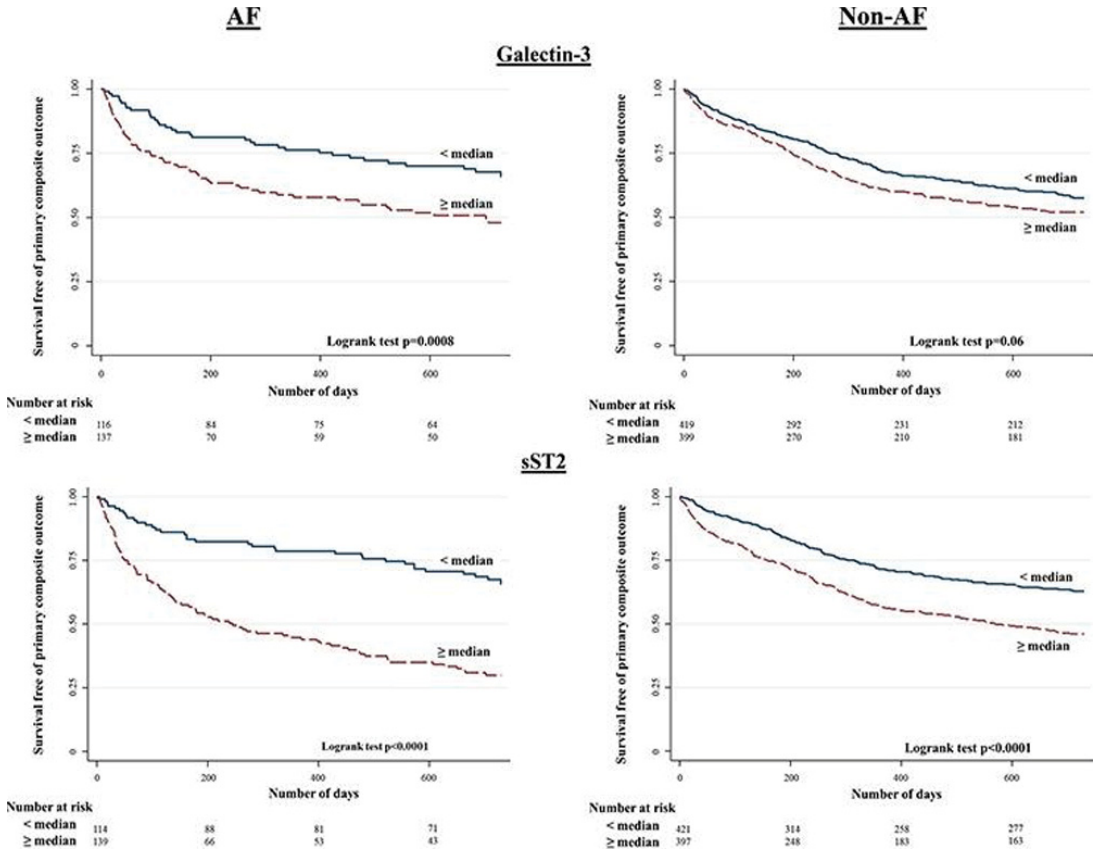


Figure 1