

1. Background

- Biomarkers are increasingly used in the *diagnosis* and *management* of patients with heart failure (HF).
- Natriuretic peptides (NPs) are strong determinants of prognosis in HF but are influenced by factors such as age, BMI, anemia and renal function.
- New biomarkers with additive value to NPs are needed, and in particular those who can predict response to therapy.
- **Galectin-3** is a newly available, FDA-cleared HF biomarker that has been suggested to be involved in the regulation of fibrogenesis and inflammation during myocardial remodeling.
- Some clinical studies have demonstrated that elevated plasma galectin-3 is associated with significantly poorer outcome in HF.

2. Aims

- To investigate the prognostic value of galectin-3 in a sub-study (comprising ~29% of participants) of the CORONA study (Controlled Rosuvastatin Multinational Trial in HF).
- To investigate whether galectin-3 defines a sub-group of CORONA HF subjects that benefits from rosuvastatin therapy.

3. Methods

- Patients (n=1462), > 60 years with systolic, ischemic HF were randomized to 10 mg/day rosuvastatin or placebo.
- Baseline plasma galectin-3 levels were determined using the FDA-approved ELISA (BG Medicine, Waltham MA); NT-proBNP was measured with a commercial assay (Roche Diagnostics, Indianapolis IN).
- End points:
 - Primary event: CV death, non-fatal MI or non-fatal stroke (n= 411)
 - Secondary: *All-cause mortality* (n= 425), *CV mortality* (n= 346); *Sudden death* (n= 196); *All-cause mort./HF hosp.* (n= 755, post-hoc).
- Data analysis:
 - For association with outcome, Cox models with covariate adjustment.
 - For differential response to rosuvastatin therapy, interaction terms between randomization group and galectin-3 value were evaluated within Cox regression models.

Support & Conflict of Interest

- The CORONA study was funded by AstraZeneca and the galectin-3 substudy was supported by a research grant from BG Medicine
- Dr Hulthe is an employee of AstraZeneca and Drs Muntendam and Adourian are employees of BG Medicine.

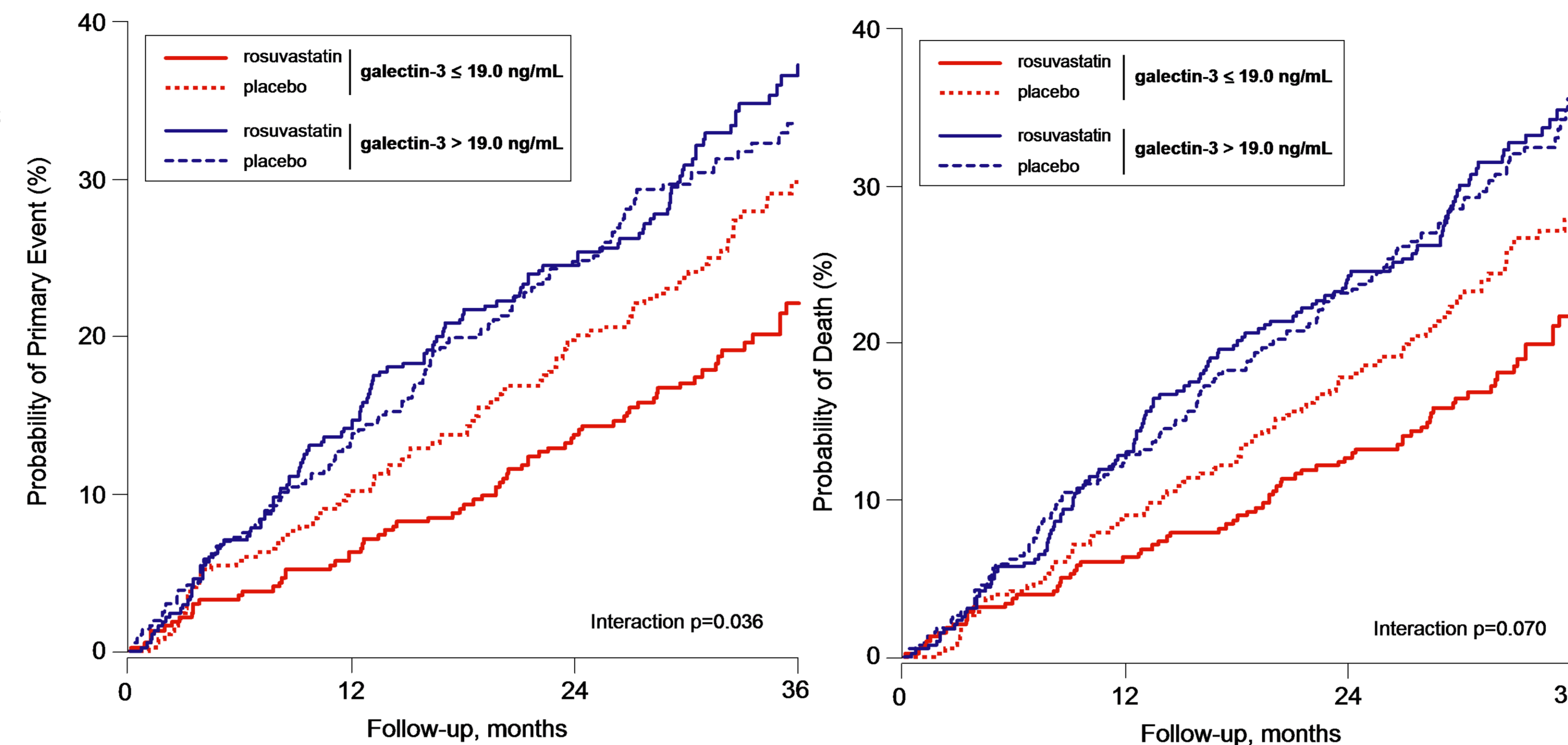


Figure 1. Kaplan-Meier survival estimates for primary endpoint (left) and for all-cause mortality (right), by galectin-3 category and by rosuvastatin/placebo randomization group.

4. Results

- Higher baseline galectin-3 levels were associated with older age, female gender, lower LVEF, lower blood pressure, higher heart rate, previous CABG or PCI, pacemaker and ICD, lower eGFR, higher NT-proBNP and CRP, and use of loop diuretics and aldosterone antagonists (Table 1).
- Elevated galectin-3 was associated with increased risk for most end points (Figure 2; univariate analysis). Adjusting for 8 clinical and 2 biochemical variables, higher galectin-3 was associated with higher risk of primary event [HR 1.16 (1.03-1.31); p=0.012] as well as all-cause and CV mortality, sudden death, and the composite of all-cause mortality and hospitalization for worsening HF. Addition of NT-proBNP attenuated this association, but an interaction was found between galectin-3 and NT-proBNP (p=0.07) yielding additive value: subjects with high baseline values of both biomarkers exhibited the poorest prognosis (Figure 3).
- There was an interaction between baseline galectin-3 and rosuvastatin on the primary endpoint (p=0.036). Among patients with galectin-3 ≤ median value of 19.0 ng/mL (n=734), rosuvastatin decreased risk of the primary endpoint compared to placebo (HR adjusted for all clinical and biochemical variables and NT-proBNP: 0.65; 95% CI, 0.46-0.92) (Figure 1); no benefit observed among subjects with galectin-3 > 19.0 ng/mL. Similar trends observed for other endpoints, including all-cause mortality.
- Consideration of both galectin-3 and NT-proBNP provided additional information, and those with galectin-3 ≤ 19.0 ng/mL and NT-proBNP ≤ median of 102.7 pmol/L exhibited a particularly low rate of primary event in the rosuvastatin group compared with the placebo group (HR: 0.33; 95% CI (0.16-0.67); p=0.002, Figure 4).

5. Conclusions

- Galectin-3 was associated with the primary endpoint and with mortality in older patients with advanced chronic systolic HF of ischemic etiology.
- Galectin-3 modified the effect of rosuvastatin, with rosuvastatin benefit accruing in subjects with baseline galectin-3 levels below 19.0 ng/mL.

Table 1. Baseline characteristics of subjects with galectin-3 measurements.

Variable	All patients with Galectin-3 values n=1462	At or below Median (≤ 19.0 ng/mL) n=734	Above Median (>19.0 ng/mL) n=728	P value
Age (yrs)	72 ± 7	70 ± 7	73 ± 7	<0.001
Female sex, no. (%)	344 (24)	146 (20)	198 (27)	0.001
NYHA class (II/III/IV) (%)	32/67/1	32/67/1	32/67/1	0.97
Ejection fraction	0.32 ± 0.07	0.32 ± 0.06	0.31 ± 0.07	0.003
Body-mass index, kg/m ²	27.2 ± 4.6	27.3 ± 4.2	27.2 ± 4.9	0.44
Systolic BP (mmHg)	130 ± 16	130 ± 15	129 ± 17	0.043
Diastolic BP (mmHg)	77 ± 9	78 ± 9	76 ± 9	<0.001
Heart rate, beats/min	71 ± 11	70 ± 11	72 ± 11	0.002
Current smoker, no. (%)	177 (12)	89 (12)	88 (12)	0.95
Hypertension	1014 (69)	510 (69)	504 (69)	0.96
Diabetes mellitus	380 (26)	176 (24)	204 (28)	0.089
Atrial fibrillation	323 (22)	148 (20)	175 (24)	0.074
Creatinine Clearance	57.66 ± 14.24	63.26 ± 12.9	52.01 ± 13.27	<0.001
NT-proBNP (median (IQR)), pmol/L	160.4 (59.6-341.4)	124.4 (45.6-263.0)	213.2 (88.7-444.2)	<0.001
CRP (median (IQR)), mg/liter	3.7 (1.6-7.7)	3.0 (1.4-6.4)	4.6 (2.1-8.9)	<0.001
Loop diuretics (%)	87	84	89	0.019
Beta blocker (%)	76	78	74	0.105
ACE inhibitor/ARB (%)	89	89	89	0.78
Aldosterone antagonist (%)	36	33	40	0.003
Digitalis/digoxin, no. (%)	419 (29)	195 (27)	224 (31)	0.086

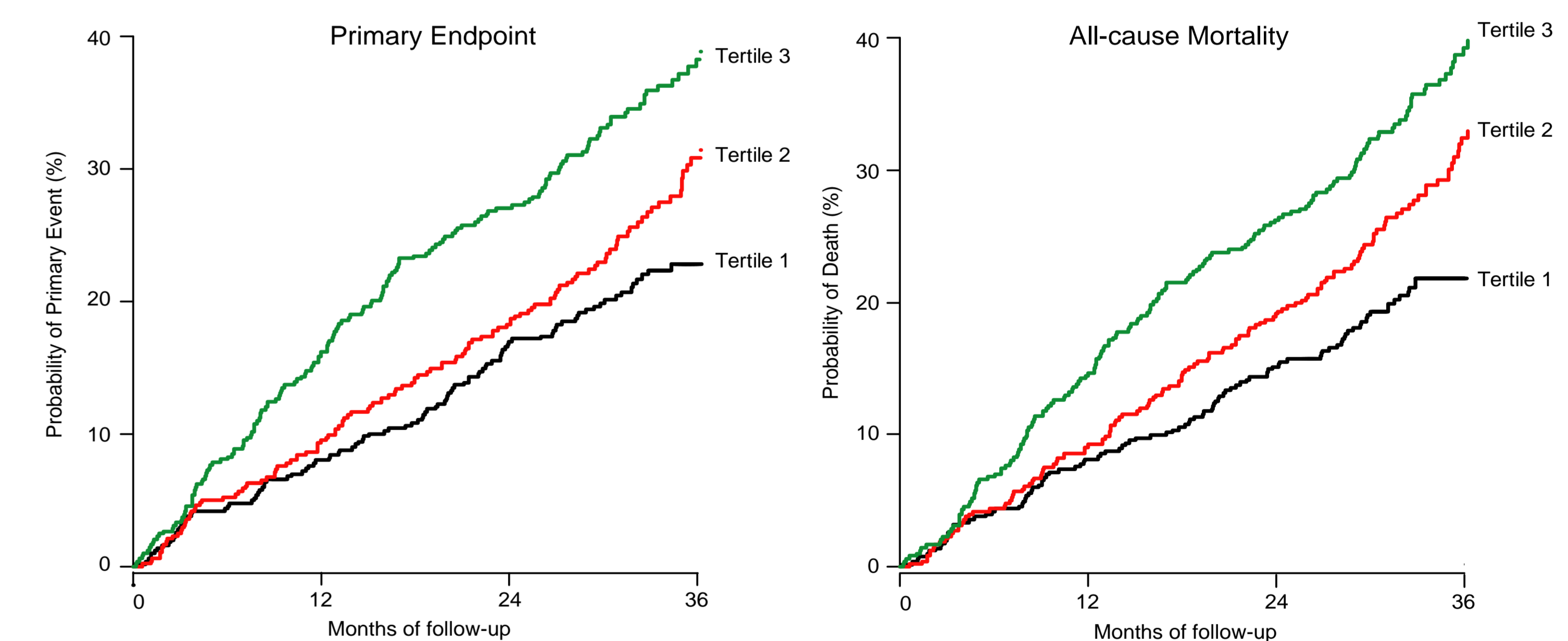


Figure 2. Kaplan-Meier survival estimates for primary endpoint (left) and for total mortality (right), by increasing tertiles of baseline galectin-3.

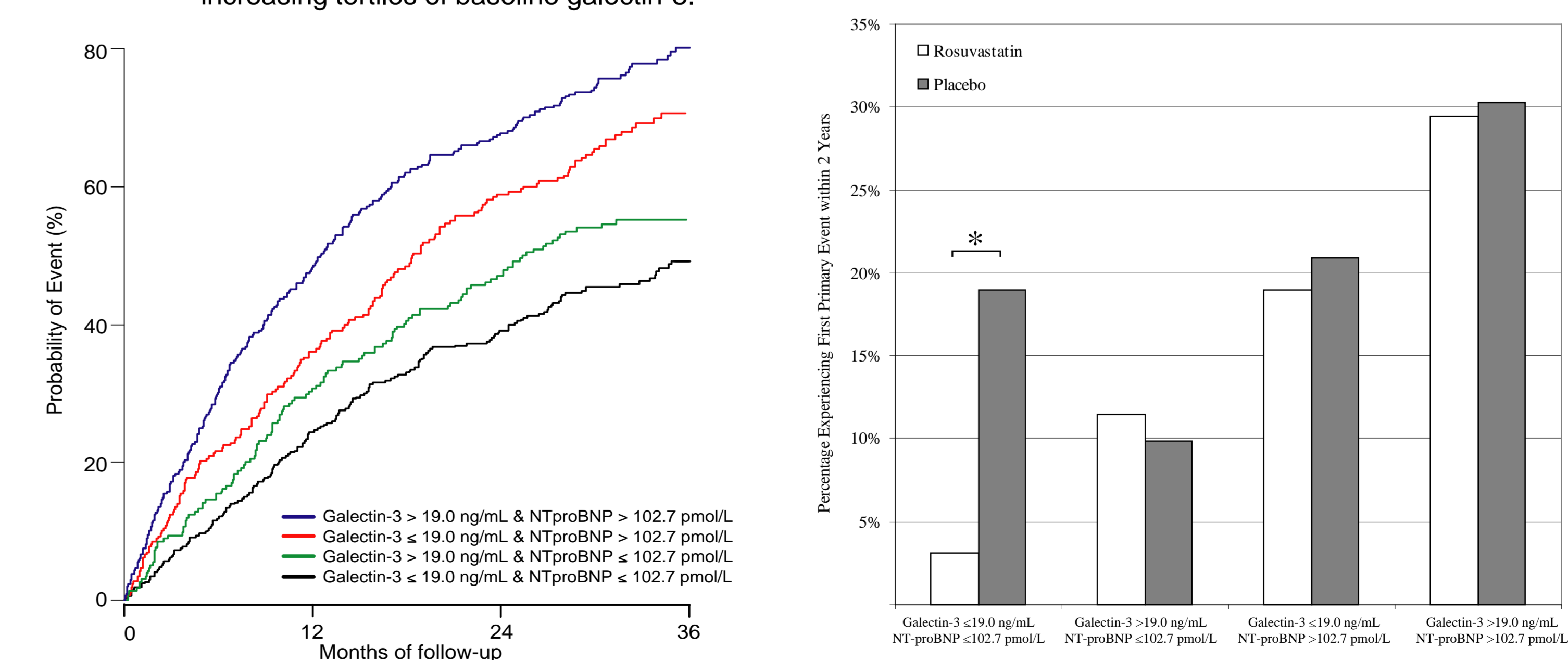


Figure 3. All-cause mortality and HF hospitalization, by joint galectin-3 and NTproBNP categories

Figure 4. Primary event rates at 2 years by treatment group, and by joint galectin-3 and NTproBNP categories