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Galectin-3 predicts response to statin therapy in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)

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Aims To investigate whether plasma galectin-3, a mediator of fibrogenesis, can identify patients with chronic heart failure (HF) for whom statins are effective.

Methods and results Patients with ischaemic systolic HF enrolled in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) were randomly assigned to 10 mg/day of rosuvastatin or placebo. Galectin-3 was measured in plasma. The primary outcome was cardiovascular death, myocardial infarction, or stroke. Of 1492 patients, 411 had a primary event during a median follow-up of 32.8 months. There was an interaction between baseline galectin-3 and rosuvastatin on the primary endpoint (*P*-value for interaction = 0.036). Among patients with below the median plasma concentrations of galectin-3 (≤19.0 ng/mL), those assigned to rosuvastatin had a lower primary event rate [hazard ratio (HR) 0.65; 95% confidence interval (CI), 0.46–0.92; *P* = 0.014], lower total mortality (HR 0.70; 95% CI, 0.50–0.98; *P* = 0.038), and lower event rate of all-cause mortality and HF hospitalizations (HR 0.72; 95% CI, 0.54–0.98; *P* = 0.017) compared with placebo, but no benefit was observed in patients with higher levels of galectin-3. The combination of concurrently low concentrations of galectin-3 and N-terminal pro-B-type natriuretic peptide (<102.7 pmol/L) identified patients with a large benefit with rosuvastatin (HR 0.33; 95% CI, 0.16–0.67; *P* = 0.002).

Conclusion Patients with systolic HF of ischaemic aetiology who have galectin-3 values <19.0 ng/mL may benefit from rosuvastatin treatment. However, the data from this *post hoc* analysis should be interpreted with caution since the overall results of the CORONA study did not show a significant effect on the primary endpoint.

Keywords Heart failure • Lipids • Cardiovascular pharmacology • Atherosclerosis • Statins

Introduction

Multiple randomized trials have shown that HMG-CoA reductase inhibitors (statins) reduce morbidity and mortality in patients with risk factors for, or clinically apparent, atherosclerotic disease, although these studies excluded (or included few) patients with heart failure (HF).[1,2] Still, various recent observational, retrospective, and subgroup analyses in HF patients have suggested a

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reduction in cardiovascular (CV) events associated with statin use also in these patients.[3,4] In contrast, two large prospective randomized placebo-controlled studies, the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)[5] and the GISSI-HF trial,[6] did not confirm this. However, additional analyses of CORONA, which enrolled older patients with chronic ischaemic systolic HF, have suggested that certain clinical or biochemical markers, reflecting underlying disease characteristics, may identify certain subgroups of HF patients that benefit from statin therapy.[7,8]

Galectin-3 is a member of a family of proteins comprising soluble β-galactoside-binding lectins that have regulatory roles in fibrogenesis, inflammation, tissue repair, and cell proliferation. Recently, it has been suggested that galectin-3 may play a role in the pathophysiology of HF through promotion of myocardial fibrosis and inflammation, two related processes involved in myocardial remodelling.[9,10] Increased galectin-3 may, therefore, be a marker for patients with a poor prognosis related to excessive and potential irreversible myocardial fibrosis. In keeping with this, several recent studies have reported an association between elevated circulating galectin-3 and poor clinical outcomes in patients with HF.[11–13]

We have recently shown that HF patients with high galectin-3 levels are characterized by more advanced myocardial failure.[14] Since statins may have a beneficial role in HF patients with low pro-B-type natriuretic peptide (proBNP),[7] reflecting less advanced disease, we sought to test the hypothesis that CORONA patients with lower galectin-3 levels, potentially reflecting lower and reversible levels of myocardial fibrosis, may show a beneficial response from rosuvastatin therapy, compared with those with higher galectin-3 concentrations.

Methods

Patients

The design and principal findings of CORONA have been reported elsewhere in detail.[5] In brief, patients >60 years with chronic HF of ischaemic cause, in New York Heart Association (NYHA) class II–IV and with left ventricular ejection fraction (LVEF) ≤40% (≤35% if NYHA II), were eligible, provided the investigator determined that they did not need treatment with a cholesterol-lowering drug. Criteria for exclusion included recent CV events, current or planned procedures, or operations; acute or chronic liver disease or alanine aminotransferase ≥2× the upper limit of normal (ULN); serum creatinine ≥2.5 mg/dL; chronic muscle disease, contraindication to statin therapy or an unexplained creatine kinase ≥2.5× ULN; thyroid stimulating hormone ≥2× ULN; and any condition substantially reducing life expectancy.

Study procedures

The trial was approved by the Ethics Committees of the participating hospitals and patients provided written informed consent. Patients were randomized to 10 mg of rosuvastatin or matching placebo, once daily. The first patient was randomized in September 2003. In the protocol, the measurement of galectin-3 was not pre-specified. However, it was pre-specified to include measurements of newer markers of inflammation that was not well known when the protocol was finished. On this basis, we initiated the present substudy of the CORONA trial, comprising 1464 consecutively included patients, to examine whether plasma levels of galectin-3 could identify patients who could benefit from rosuvastatin therapy.

Study outcomes and definitions

The primary pre-defined outcome was the composite of CV mortality, non-fatal myocardial infarction (MI), or non-fatal stroke, analysed as time to the first event. The secondary outcomes included all-cause mortality, any coronary event (defined as sudden death, fatal or non-fatal MI, PCI, CABG, ventricular defibrillation by an ICD, resuscitation from cardiac arrest or hospitalization for unstable angina), cardiovascular mortality (with an additional analysis of cause-specific death from a cardiovascular cause) and number (episodes) of hospitalizations (for cardiovascular causes, unstable angina and worsening heart failure). The additional *post hoc* composite outcome of death resulting from any cause or hospitalization for worsening HF was also considered. Definition and adjudication of all outcomes have been described in detail previously.[5]

Blood sampling and biochemical analyses

Blood samples were non-fasting, except for galectin-3, and analysed on stored samples at a central laboratory (Medical Research Laboratories, Zaventem, Belgium). Plasma cholesterol, creatinine, N-terminal proBNP (NT-proBNP) and high-sensitivity C-reactive protein were analysed as described previously.[7,8] Plasma galectin-3 levels were determined on stored specimens (stored at −80°C, thawed once) using an enzyme-linked immunosorbent assay (BG Medicine, Waltham, MA, USA) according to the manufacturer's instructions.

Statistical analysis

For the main objective of investigating the effects of rosuvastatin treatment according to the baseline galectin-3 level, galectin-3 categories were defined based on the median baseline value across all 1462 subjects for whom a galectin-3 measurement was available. For each of six endpoints, a formal interaction test was conducted with a Cox proportional hazards model comprising treatment group (binary variable), galectin-3 category (dichotomous variable), and the interaction term. The endpoints investigated were not independent (e.g. the primary composite endpoint comprised CV mortality, and CV mortality was investigated separately as well). Subsequently, the Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) comparing rosuvastatin and placebo treatments by galectin-3 categories. Fully adjusted models included the following 11 pre-specified covariates as previously determined,[15] all evaluated at baseline: age (per year), gender, LVEF (per unit), NYHA class (due to the small number of subjects with class IV, classes III and IV were combined), body mass index (per unit), diabetes mellitus (yes/no), intermittent claudication (yes/no), heart rate (per unit), estimated glomerular filtration rate (eGFR) (per unit), the ratio of apolipoprotein B to apolipoprotein A1, [$\log_e$]NT-proBNP, and high-sensitivity C-reactive protein. Incident event rates were analysed using the Poisson regression. Baseline characteristics were compared by the galectin-3 category using Student's *t*-test for variables expressed as means and standard deviation (SD), by Wilcoxon's rank-sum test for variables expressed as median and inter-quartile range (IQR), and by the χ^2 test for variables expressed as percentages (except for NYHA class, for which the Fisher's exact test was used). Correlation coefficients were calculated with the use of age-adjusted Pearson's partial-correlation coefficients. All *P*-values are two-tailed. All analyses were performed with SAS software, version 9.1 (SAS Institute), or R software, version 2.

Results

Of the 5011 patients enrolled in the CORONA study, 1462 (29%) subjects had a baseline plasma specimen available for measurement of galectin-3. Compared with the entire CORONA population, the patients in the present study were slightly younger, more patients were in NYHA class III, they had higher LVEF, higher diastolic blood pressure, and higher cholesterol levels, and more patients had hypertension and had a previous MI, while fewer patients had diabetes mellitus and fewer had pacemaker (see Supplementary material online, *Table S1*). The clinical characteristics for this substudy population as a whole and by the median baseline galectin-3 value of 19.0 ng/mL are shown in *Table 1*. Older age, female gender, lower LVEF, lower blood pressure, higher heart

Table 1 Baseline characteristics of subjects with galectin-3 measurements

Variable	All patients with galectin-3 values ($n = 1462$)	Below median (≤19.0 ng/mL) ($n = 734$)	Above median (>19.0 ng/mL) ($n = 728$)	*P*-value[a]
Age (years)	72 ± 7	70 ± 7	73 ± 7	<0.001
Female sex, *n* (%)	344 (24)	146 (20)	198 (27)	0.001
NYHA class, *n* (%)				0.97
II	469 (32)	234 (32)	235 (32)	
III	976 (67)	491 (67)	485 (67)	
IV	17 (1)	9 (1)	8 (1)	
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 (b.p.m.)	71 ± 11	70 ± 11	72 ± 11	0.002
Current smoker, *n* (%)	177 (12)	89 (12)	88 (12)	0.95
Medical History, *n* (%)				
Myocardial infarction	921 (63)	445 (61)	476 (65)	0.067
CABG or PCI	304 (21)	134 (18)	170 (23)	0.020
Hypertension	1014 (69)	510 (69)	504 (69)	0.96
Diabetes mellitus	380 (26)	176 (24)	204 (28)	0.089
Current atrial fibrillation or flutter on ECG	323 (22)	148 (20)	175 (24)	0.074
Stroke	175 (12)	80 (11)	95 (13)	0.24
Pacemaker	135 (9)	52 (7)	83 (11)	0.006
Implantable cardioverter-defibrillator	39 (3)	12 (2)	27 (4)	0.022
Total cholesterol (mmol/L)	5.23 ± 1.09	5.23 ± 1.05	5.23 ± 1.13	0.93
LDL cholesterol (mmol/L)	3.64 ± 0.98	3.66 ± 0.92	3.63 ± 1.04	0.50
HDL cholesterol (mmol/L)	1.23 ± 0.34	1.24 ± 0.33	1.22 ± 0.35	0.33
Triglycerides (mmol/L)	2.01 ± 1.39	1.95 ± 1..37	2.07 ± 1.41	0.099
eGFR	57.66 ± 14.24	63.26 ± 12.9	52.0 ± 13.3	<0.001
ApoB:ApoA1 ratio	0.89 ± 0.25	0.87 ± 0.24	0.9 ± 0.26	0.057
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
C-reactive protein [median (IQR)] (mg/L)	3.7 (1.6–7.7)	3.0 (1.4–6.4)	4.6 (2.1–8.9)	<0.001
Loop diuretics, *n* (%)				0.019
0	191 (13)	114 (16)	77 (11)	
1	1111 (76)	543 (74)	568 (78)	
2	160 (11)	77 (10)	83 (11)	
β-Blocker, *n* (%)	1112 (76)	572 (78)	540 (74)	0.105
ACE-inhibitor, *n* (%)	1178 (81)	590 (80)	588 (81)	0.90
Aldosterone antagonist, *n* (%)	532 (36)	239 (33)	293 (40)	0.003
Digitalis/digoxin, *n* (%)	419 (29)	195 (27)	224 (31)	0.086

[a]*P*-values for the difference across galectin-3 categories are determined by Student's *t*-test for continuous variables expressed as mean ± 1 SD and by the χ^2 test for variables expressed as percentages except for NYHA class for which Fisher's exact test was used.

rate, previous CABG or PCI, implanted pacemaker and ICD, lower eGFR, higher NT-proBNP and high-sensitivity C-reactive protein levels, and the current use of loop diuretics and aldosterone antagonists were associated with high galectin-3 levels. The prevalence of smoking, hypertension, and diabetes, as well as distribution of NYHA classes and the use of β-blockers and angiotensin-converting enzyme inhibitors, was similar in the two galectin-3 groups. When using galectin-3 as a continuous variable in a stepwise multiple linear regression analyses including all associated variables from *Table 1*, we found that increased galectin-3 levels were significantly and independently associated with older age, female sex, low eGFR, high log high-sensitivity C-reactive protein, high log NT-proBNP, and the use of aldosterone antagonists (adjusted $R^2 = 0.27$), but not the other variables, suggesting that these variables are those that are most closely associated with galectin-3.

Baseline galectin-3 levels were similar among subjects randomized to rosuvastatin ($n = 737$; median, 19.1 ng/mL; IQR, 15.5–23.6 ng/mL) and to placebo ($n = 725$; median, 18.9 ng/mL; IQR, 15.6–23.9 ng/mL; $P = 0.85$ compared with the rosuvastatin group). There were no differences in clinical or biochemical variables between patients receiving rosuvastatin or placebo, or within each randomization group (data not shown).

Interaction between the effects of rosuvastatin treatment and galectin-3

There was an interaction between the baseline galectin-3 category and the effect of rosuvastatin on the primary endpoint of CV death, non-fatal MI, and non-fatal stroke ($P = 0.036$ for interaction). Among subjects with baseline galectin-3 less than or equal to the median value of 19.0 ng/mL ($n = 734$), rosuvastatin treatment was associated with a decreased risk of the primary endpoint compared with placebo (HR adjusted for all 11 clinical and biochemical variables and NT-proBNP: 0.65; 95% CI, 0.46–0.92; $P = 0.014$ after adjustment) (*Figures 1* and *2A*). In this low baseline galectin-3 group, the rate of primary events among subjects randomized to rosuvastatin was 7.8 events per 100 patient-years, compared with 11.2 events per 100 patient-years of follow-up in the placebo group, representing a 30.4% difference ($P = 0.019$ for comparison of rates). In contrast, among subjects with baseline galectin-3 levels >19.0 ng/mL ($n = 728$), rosuvastatin treatment was not associated with benefit compared with placebo (adjusted HR, 1.07; 95% CI, 0.79–1.45; $P = 0.66$), and event rates were comparable (15.1 events per 100 patient-years in the rosuvastatin group, compared with 14.2 events per 100 patient-years in the placebo group, $P = 0.61$). An effect was observed for total mortality and the combined endpoint of total mortality and hospitalization for worsening HF, but not for the other endpoints (*Figure 1*). Additionally, an effect was also found when combining the two non-fatal variables in the primary endpoint (i.e. non-fatal MI and non-fatal stroke) (adjusted HR: 0.43; 95% CI, 0.23–0.80; $P = 0.007$). A similar pattern was seen when including each of the two non-fatal endpoints separately, but in general, the number of events was too low to achieve reliable results (data not shown). The Kaplan–Meier probability estimates by the treatment group and by the baseline galectin-3 level are shown for the primary endpoint and for total mortality in *Figure 2A* and *B*, respectively.

Effects of rosuvastatin in patients with low levels of galectin-3 and N-terminal pro-B-type natriuretic peptide and in patients with low galectin-3 and low high-sensitivity C-reactive protein levels

Low NT-proBNP (cut-off 102.7 pmol/L) and high high-sensitivity C-reactive protein (cut-off 2 mg/L) have previously been shown to be associated with beneficial effects of rosuvastatin in the CORONA study.[7,8] We therefore next examined the interaction of galectin-3 with these two variables. Not surprisingly, based on the strong correlations between these three parameters (*Table 1*), there was some overlap between their quartiles (i.e. more patients in lower high-sensitivity C-reactive protein and NT-proBNP quartiles among patients in the lowest than in the highest galectin-3 quartile etc.) (see Supplementary material online, *Table S2*). Moreover, among the 734 subjects with the baseline galectin-3 level of ≤19.0 ng/mL, 631 subjects also had a baseline measurement of NT-proBNP. Using 102.7 pmol/L (868 pg/mL) as a cut-off value for NT-proBNP, 277 of the 631 subjects (43.9%) in the low galectin-3 group also had a low baseline NT-proBNP value. This group of subjects, characterized by low values on both parameters, exhibited a particularly low rate of the primary event in the rosuvastatin group compared with the placebo group (HR, 0.33; 95% CI, 0.16–0.67; $P = 0.002$; *Table 2*; see Supplementary material online, *Figure S1*). A lower rate of total mortality was also observed in the rosuvastatin, compared with placebo, group in these subjects (HR, 0.38; 95% CI, 0.19–0.76; $P = 0.006$). We also looked at other combination of cut-off values for NT-proBNP and galectin-3 (divided according to tertiles, quartiles, or optimal cut-off derived from receiver-operating characteristic analysis), but these values did not give any additional information. In addition, lower cut-off for NT-proBNP than 102.7 pmol/L was not superior to the combination of low proBNP and low galectin-3 to identify those who could benefit from statin therapy (data not shown). Combining galectin-3 and high-sensitivity C-reactive protein, using 2 mg/L as a cut-off value for high-sensitivity C-reactive protein, showed an effect of rosuvastatin compared with placebo in the group with low galectin-3 and low high-sensitivity C-reactive protein (0.55; 95% CI, 0.31–0.99; $P = 0.046$), but not in the other groups (see Supplementary material online, *Figure S1*).

Change in lipids and lipoproteins during follow-up

In each of the galectin-3 categories, dichotomized by the median value of 19.0 ng/mL, rosuvastatin treatment resulted in a similar change from baseline to the 3-month follow-up visit in the levels of low-density lipoprotein cholesterol (LDL-C), triglycerides, high-density lipoprotein cholesterol (HDL-C), total cholesterol, and the ratio of apolipoprotein B to apolipoprotein A1. The mean percentage change in LDL-C with rosuvastatin treatment was −43.3% in the low galectin-3 group and −43.2% in the high galectin-3 group ($P = 0.74$ for comparison); for triglycerides, −12.8 and −15.9% ($P = 0.40$); for HDL-C, 6.3 and 4.5% ($P = 0.18$); for total cholesterol, −22.2 and −26.8% ($P = 0.73$); and for the ratio of apolipoprotein B to apolipoprotein A1, −36.3 and −35.7% ($P = 0.64$).

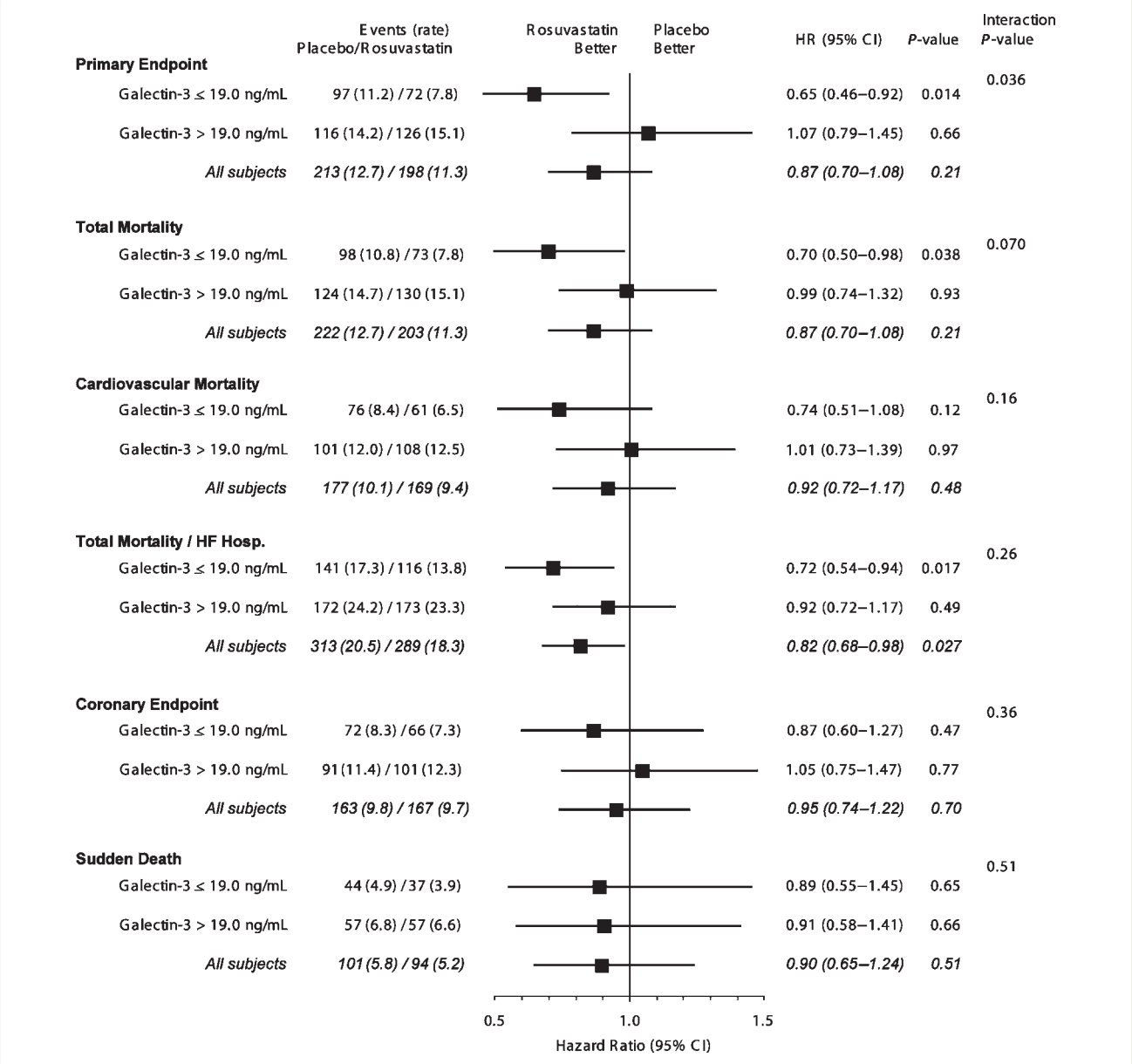

Figure 1 Interactions between galectin-3 categories (above and at or below the median level, 19.0 ng/mL) and rosuvastatin on endpoints. Event counts, event rates, and hazard ratios and 95% confidence intervals in the galectin-3 categories, the interaction *P*-value, and *P*-values for each subgroup are shown. Hazard ratios are adjusted for the following baseline covariates: age, gender, New York Heart Association class, estimated glomerular filtration rate, left ventricular ejection fraction, body mass index, history of diabetes mellitus, history of intermittent claudication, heart rate, the ratio of apolipoprotein B to apolipoprotein A1, and N-terminal pro-B-type natriuretic peptide. HR, hazard ratio; CI, confidence interval. The primary endpoint is a composite of cardiovascular death and non-fatal myocardial infarction and stroke, and the coronary endpoint is a composite of sudden death, fatal or non-fatal myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, ventricular defibrillation by an implantable cardioverter-defibrillator, resuscitation from cardiac arrest, or hospitalization for unstable angina.

Discussion

The main finding of this study is that circulating galectin-3 potentially may help identify a subset of HF patients with ischaemic heart disease and chronic LV systolic dysfunction who might benefit from treatment with statins. It has been speculated that statins, by promoting angiogenesis, improving endothelial function, and exerting a net anti-inflammatory effect on the cytokine network, might be of clinical benefit in HF.[16] Indeed, until the publication of GISSI-HF and CORONA, observational data had supported a possible beneficial effect of statins in HF. However, two large, prospective, randomized trials, CORONA and GISSI-HF,[5,6]

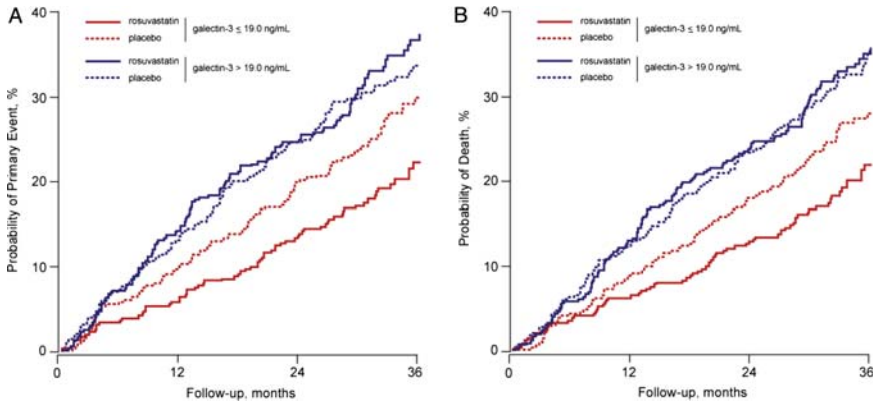

Figure 2 The Kaplan–Meier estimates for the primary endpoint (cardiovascular death and non-fatal myocardial infarction and stroke) (*A*) and for total mortality (*B*) by galectin-3 category (above and at or below the median level, 19.0 ng/mL). Rosuvastatin treatment was associated with a significantly decreased risk of the primary endpoint compared with placebo (hazard ratio adjusted for clinical variables, estimated glomerular filtration rate, lipid parameters, and N-terminal pro-B-type natriuretic peptide: 0.65; 95% confidence interval, 0.46–0.92; $P = 0.014$ and for total mortality: 0.70; 95% confidence interval, 0.50–0.98; $P = 0.038$) among subjects with baseline galectin-3 less than or equal to the median value of 19.0 ng/mL ($n = 734$).

Table 2 Rate of subjects experiencing the primary events by 1 year by joint galectin-3 and N-terminal pro-B-type natriuretic peptide categories

	n	Placebo, rate (95% CI) (per 100 person-years)	Rosuvastatin, rate (95% CI) (per 100 person-years)	*P*-value
Galectin-3 ≤19.0 ng/mL, NT-proBNP ≤102.7 pmol/L	277	8.8 (5.6–11.9)	2.9 (1.1–4.7)	0.002
Galectin-3 ≤19.0 ng/mL, NT-proBNP >102.7 pmol/L	354	13.5 (9.9–17.0)	11.2 (8.0–14.4)	0.36
Galectin-3 >19.0 ng/mL, NT-proBNP ≤102.7 pmol/L	172	5.5 (2.5–8.5)	4.6 (1.6–7.6)	0.69
Galectin-3 >19.0 ng/mL, NT-proBNP >102.7 pmol/L	410	17.3 (13.2–21.5)	19.1 (15.1–23.1)	0.54

Primary endpoint (expressed as rate per 100 patient-years of follow-up) according to the baseline plasma galectin-3 and NT-proBNP concentration category. Galectin-3 is dichotomized by the median concentration of 19.0 ng/mL and NT-proBNP by a previously identified cut-point of 102.7 pmol/L.

refuted these findings and, as a result, the general use of statins in patients with HF is not recommended. It remains, however, possible that statins might be beneficial in certain subgroups of patients with HF, and to date, this hypothesis has been proposed for subjects with a low NT-proBNP or high high-sensitivity C-reactive protein concentration.[7,8] Our data in the present study may suggest that HF patients with low baseline galectin-3 levels could also benefit from rosuvastatin. Using the combination of galectin-3 and NT-proBNP to select candidates for therapy may be particularly useful as, in the present study, patients with low levels on both parameters demonstrated the lowest rate of adverse outcomes with rosuvastatin treatment.

Why the low plasma concentration of galectin-3 should identify a subset of patients who may benefit from rosuvastatin is at present not clear. It is not explained by a differential lipid-lowering effect in the two galectin-3 groups. Previously, the possible benefit of statins in patients with lower NT-proBNP concentrations was suggested to be related to patients with less severe systolic dysfunction, possibly due to less myocyte loss as a result of infarction/ischaemia. Low NT-proBNP and low galectin-3 may, however, identify different patient groups. While the beneficial effect of rosuvastatin in patients with low NT-proBNP reflected fewer atherothrombotic events and sudden deaths,[7] this seems not to be the case for patients with low galectin-3 levels. Thus, we could not relate the beneficial effect of rosuvastatin in patients with low galectin-3 levels to decreased coronary endpoints or sudden death. As galectin-3 is thought to play an integral role in tissue fibrosis, it may be that patients with low plasma galectin-3 levels are those with less myocardial fibrosis and potentially more viable myocardium that may be protected by statin therapy. Unfortunately, we could not test this hypothesis further as serial cardiac imaging studies were not performed in CORONA and we do not have any measurements of post-randomization LV volumes, systolic or diastolic function, and no assessment of myocardial collagen content at baseline or later.

Previous studies have suggested that HF patients with high levels of high-sensitivity C-reactive protein could benefit from rosuvastatin therapy.[8] As galectin-3 levels is also thought to reflect

inflammatory pathways, this may seem in conflict with the present study, showing that low galectin-3 levels are associated with beneficial effects of rosuvastatin. The reasons for this apparently discrepancy are not clear, but could reflect that C-reactive protein and galectin-3 mirror different up-stream inflammatory pathways. It is also possible that the association of low galectin-3 levels with beneficial effects of statins is primarily related to the potential ability of low galectin-3 levels to reflect reversible as opposed to irreversible myocardial fibrosis. Our findings of a beneficial effect of rosuvastatin in patients with low high-sensitivity C-reactive protein and low galectin-3 levels further suggest that these parameters could reflect distinct pathways in the pathogenesis of chronic HF. However, the data should be interpreted with caution with a relative low number of patients in each of the four subgroups.

Limitations

The strength of the present study lies in the well-defined and well-characterized patient population, as well as the thorough outcome adjudication of the CORONA study. The present study examined multiple endpoints in a large HF population with a considerable number of events. However, for some subgroup analyses, event rates were limited, and the data should be interpreted cautiously. Moreover, the data from this *post-hoc* analysis should be interpreted with caution since the overall results of the CORONA study did not show a significant effect on the primary endpoint. Another limitation is that the present substudy included only 1462 patients of the total CORONA population of 5011 patients with some significant differences in baseline characteristics. In addition, the population comprised subjects aged 60 years and older who had high prevalence co-morbidities that are common in elderly patients, and the results cannot necessarily be applied to a general HF population. In addition, patients considered were diagnosed with systolic HF and our findings may not apply to patients with preserved LVEF. The analysis in the present study is retrospective, and ideally prospective testing of a statin in HF patients with low baseline galectin-3 would be carried out.

Conclusions

We hypothesize that in patients with chronic HF and LV systolic dysfunction due to ischaemic heart disease, lower plasma concentrations of galectin-3 may identify those who benefit from statin therapy. However, our data must be interpreted with caution as hypothesis generating and will have to be confirmed in larger forthcoming studies.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: J.K., J.J.V.M., J.G.F.C and L.G. have received lecture fees from AstraZeneca. J.W., besides his position as Assistant Director, Wallenberg Laboratory for Cardiovascular Research, Sahlgrenska Academy, Gothenburg University, Sweden also was a former advisor on cardiovascular research at AstraZeneca CV Research Laboratories, Mölndal, Sweden. J.H. is an employee at AstraZeneca. P.M. and A.A. are employees and shareholders of BG Medicine Inc. which has certain rights to galectin-3. D.J.V.V. has received consultancy fees from BG Medicine.

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