



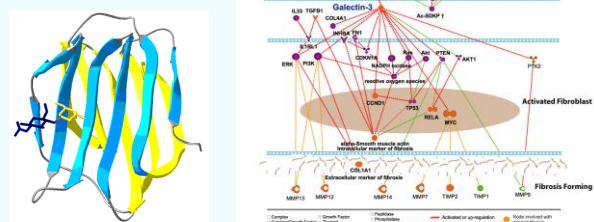
# Galectin-3, cardiovascular risk factors, and outcome in the general population



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## Introduction and Aim

Galectin-3, a biomarker of fibrosis and inflammation, predicts outcome in subjects with heart failure. The association of galectin-3 with cardiovascular (CV) risk factors and mortality in the general population remains to be established.



## Methods

We studied 7,968 subjects from the general population (derived from the Prevention of Renal and Vascular End-stage Disease study). At baseline, subjects were extensively phenotyped for all CV risk factors. We measured baseline plasma galectin-3 levels with an ELISA. All cause mortality was recorded, with a median follow-up of ~10 years.

## Results

Galectin-3 levels were associated with age, gender, diabetes, hypertension, hypercholesterolemia, body mass index, renal function (all  $P < 0.001$ ), and smoking ( $P = 0.002$ ). The effect of hypertension, hypercholesterolemia and body mass index on galectin-3 levels was modified by gender (P for interaction  $< 0.001$ ) with females having stronger associations. Subjects were then categorized in quintiles according to their galectin-3 levels. Galectin-3 levels predicted all-cause mortality (total mortality:  $N = 614$ , 7.7%), as shown in the Kaplan Meier curve. The green line represents the lowest quintile, and the red line represents the highest quintile. We observed increased risk for each quintile (Chi-square 168,  $P < 0.001$ ). After adjustment for classical CV risk factors, galectin-3 levels still predicted all-cause mortality (per doubling of galectin-3: HR 1.23, 95%CI 1.01-1.48;  $P = 0.036$ ).

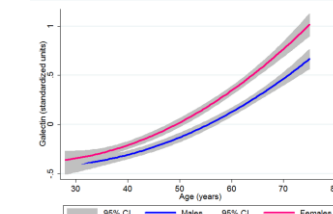
Table 1. Baseline characteristics

	Total (n=7968)	1	2	3	4	5	P
Median [IQR] galectin (ng/ml)	11.4 (8-15.1)	7.7 (7-26)	9.4 (8-9.8)	10.9 (10.5-11.3)	12.6 (12.2-13.1)	15.6 (14.5-17.7)	
Age	49.52±12.7	44.4±11.1	45.9±11.3	48.8±12.0	52.1±12.6	56.4±12.9	0.000
Female gender	50.2	47.4	48.9	48.5	50.6	56.1	0.000
Smoking (last 5 yrs), %	44.6	47.4	46.5	44.5	44.6	40.8	0.002
DM, %	3.6	2.3	2.5	3.1	4.5	6.1	0.000
MI	2.7	1.8	2.4	2.7	4.2	7.4	0.000
Hypertension	33.4	22.2	26.6	31.1	39.7	47.9	0.000
TC	54.3	24.8	29.7	34.7	39.6	43.9	0.000
Stroke, %	0.9	0.8	0.6	0.6	1.0	1.6	0.004
WHR	0.88±0.10	0.87±0.10	0.87±0.10	0.88±0.10	0.89±0.09	0.90±0.09	0.000
BMI	26.1±4.20	25.1±4.9	25.5±5.0	26.2±4.1	26.8±4.8	27.5±4.4	0.000
Systolic BP	119.2±13.2	115.0±13.1	116.6±13.0	118.6±13.6	121.3±13.6	124.9±13.5	0.000
Diastolic BP	74.6±9.7	72.1±9.4	73.3±9.8	74.1±9.6	75.2±9.8	75.4±9.8	0.000
Cholesterol	5.66±1.12	5.41±1.05	5.56±1.10	5.68±1.11	5.79±1.11	5.91±1.17	0.000
LDL	5.49±1.09	5.47±1.00	5.60±1.03	5.71±1.04	5.77±1.05	5.90±1.06	0.000
HDL	1.27 [1.09-1.56]	1.31 [1.07-1.62]	1.30 [1.06-1.57]	1.29 [1.06-1.55]	1.24 [1.00-1.53]	1.20 [0.99-1.52]	0.000
Triglycerides	1.14 [0.85-1.45]	1.02 [0.75-1.45]	1.11 [0.82-1.19]	1.17 [0.88-1.66]	1.25 [0.89-1.75]	1.31 [0.95-1.82]	0.000
Glucose	4.7 [4.4-5.1]	4.6 [4.3-5.0]	4.7 [4.3-5.1]	4.7 [4.3-5.1]	4.8 [4.4-5.2]	4.9 [4.5-5.3]	0.000
Creatinin	82 [74-92]	86 [75-89]	81 [72-90]	83 [74-92]	84 [74-93]	84 [75-97]	0.000
Cystatin-C	0.78 [0.69-0.88]	0.79 [0.69-0.82]	0.79 [0.67-0.83]	0.77 [0.69-0.87]	0.80 [0.72-0.90]	0.80 [0.74-1.00]	0.000
MDRD	90 [79-99]	86 [76-93]	87 [79-93]	89 [79-99]	79 [69-96]	79 [68-93]	0.000
UAE	9.5 [4.1-17.5]	9.1 [4.4-17.5]	8.8 [4.2-14.9]	9.1 [6.5-17.2]	10.2 [6.5-19.7]	10.4 [6.4-24.2]	0.000
hs-CRP	1.29 [0.56-3.00]	0.89 [0.39-2.14]	1.04 [0.49-2.40]	1.33 [0.58-2.92]	1.53 [0.71-3.42]	1.88 [0.85-4.26]	0.000
NT-proBNP	58.6 [17.4-74.9]	32.8 [15.4-41.4]	52.1 [14.7-62.2]	57.2 [16.4-71.1]	45.5 [19.4-62.8]	52.7 [25.2-108.0]	0.000

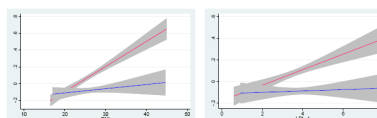
DM, Diabetes Mellitus; MI, Myocardial infarction; WHR, Waist-hip ratio; BMI, Body Mass Index; TC, Total cholesterol; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; TG, Triglycerides; MDRD, Modified Diet and Renal Disease formula; UAE, urinary albumin excretion rate (mg/24 hours); hs-CRP, high sensitivity C-reactive protein (mg/L); NT-proBNP, N-terminal pro-brain natriuretic peptide (pg/mL).

Table S2. Number of times each variable is selected after 1000 bootstrap samples

Variable	Number of times selected
Age	417
Age <sup>2</sup>	95
Sex	1000
DM	500
MI	415
HT	119
TC	388
Stroke	278
WHR	189
BMI	1000
Systolic BP	179
Diastolic BP	403
LDL	167
HDL	108
Triglycerides	218
Glucose	1000
Creatinin	1000
Cystatin-C	1000
UAE	107
hs-CRP	979
NT-proBNP	284



A. SEX\*BMI interaction



Variable	Beta +/- SE	Std(beta)	P-value
AGE <sup>2</sup>	0.00019±28.96e-06	0.243	3.90 e-94
Sex	0.317±0.025	0.159	8.17 e-41
BMI	0.014±0.003	0.059	3.91 e-07
Triglycerides	0.058±0.012	0.057	3.60 e-07
Creatinin	0.007±0.0007	0.131	1.67 e-21
Cystatin-C	0.533±0.064	0.112	6.11 e-17
CRP	0.010±0.002	0.053	1.08 e-06

Standardized B (Std-B) reflects the change in the dependent variable for 1-SD change in the independent variable. A large Std-B reflects greater strength of the association

## Results (continued)

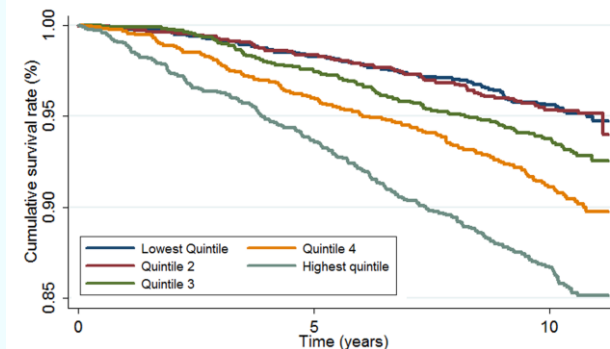


Table 4. Galectin-3 and risk of mortality

Model	All cause		Cardiovascular		Cancer	
	HR [95% CI]	P-value	HR [95% CI]	P-value	HR [95% CI]	P-value
Unadjusted	1.46 (1.37-1.56)	0.000	1.56 (1.39-1.75)	0.000	1.41 (1.28-1.56)	0.000
Age and sex adjusted	1.12 (1.03-1.21)	0.007	1.16 (1.01-1.35)	0.044	1.10 (0.97-1.23)	0.128
Multivariable classical risk factor adjusted*	1.09 (1.01-1.19)	0.036	1.10 (0.94-1.28)	0.228	1.08 (0.96-1.22)	0.222

HR indicates hazard ratio per SD change in galectin-3. \* the multivariable model included age, sex, hypertension, hypercholesterolemia, diabetes, and smoking.

## Conclusions

Galectin-3 levels are associated with CV risk factors and this effect is modified by gender. Higher galectin-3 levels are associated with increased mortality rates in the general population. This underscores the potential involvement of galectin-3 in CV disease.

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**Conflicts of interest:** Drs. Van Veldhuisen and de Boer received honoraria from BG Medicine (speakers fee, consultancy). BG Medicine provided research grants to the UMC Groningen, the employer of Drs. van Veldhuisen and de Boer.