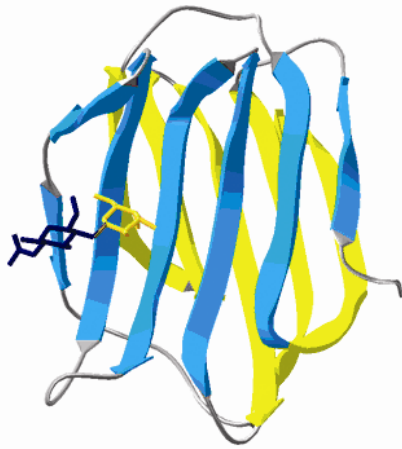
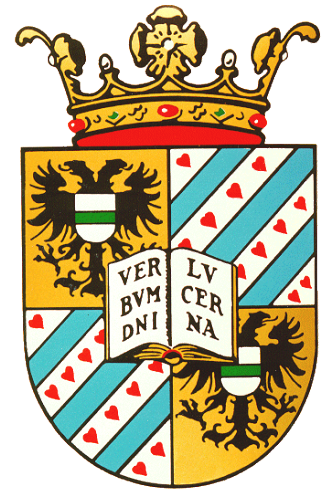


Galectin-3 and cardiovascular outcomes in patients with end-stage renal disease

Data from the German Diabetes and Dialysis Study



Rudolf A. de Boer MD
Christoph Wanner MD *
Katja Blouin MSc *
Christiane Drechsler MD *



Department of Cardiology, University Medical Center Groningen, The Netherlands and
* Department of Medicine, Division of Nephrology, University Hospital Würzburg, Germany



Background

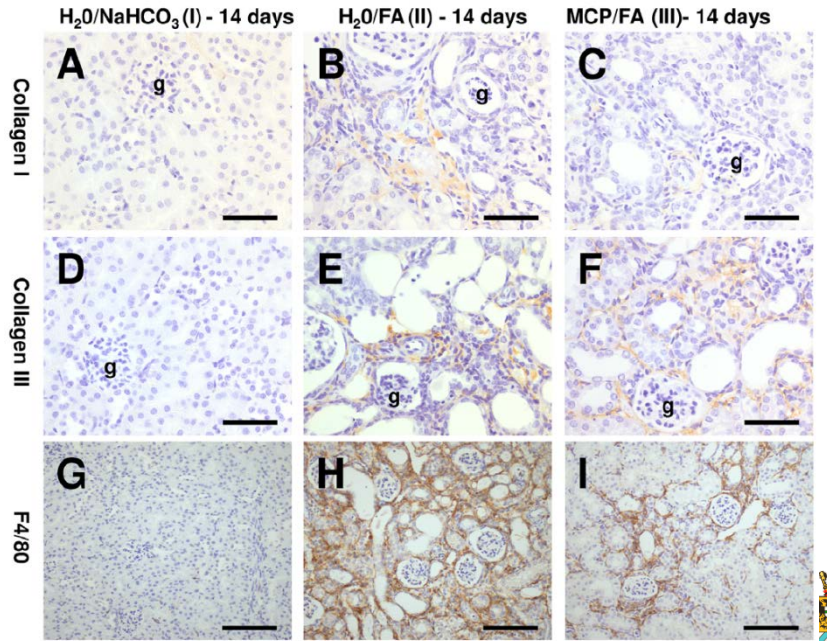
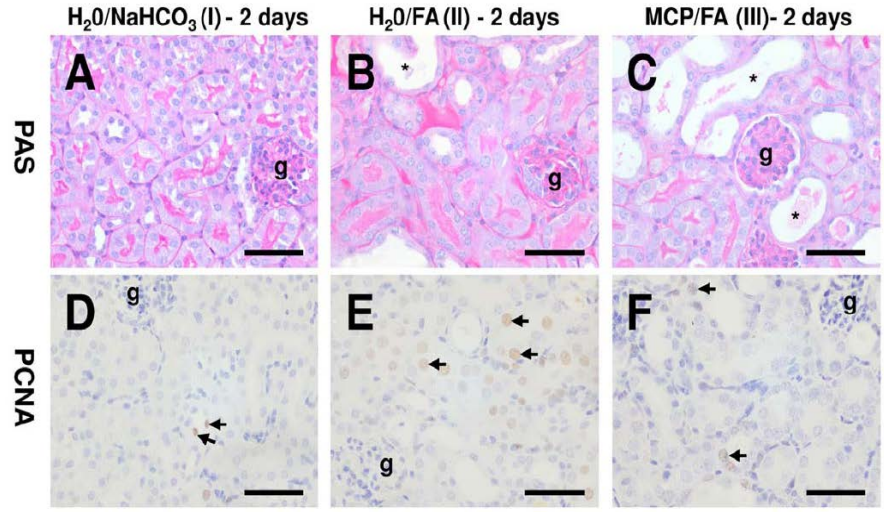
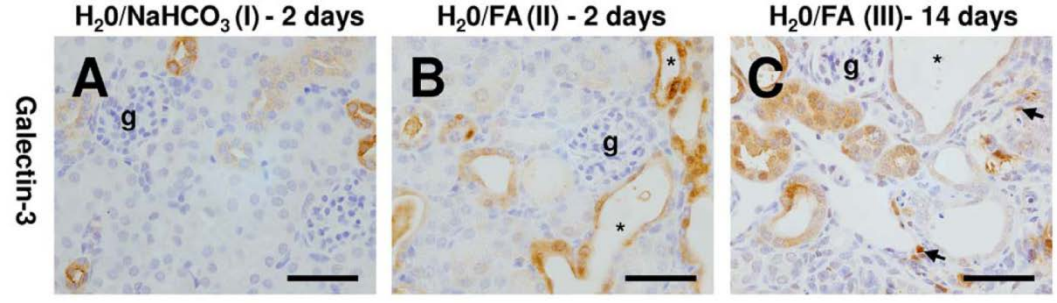
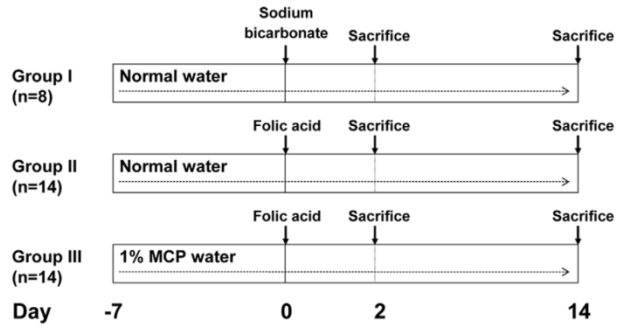
- Galectin-3 is a soluble beta-galactoside binding lectin involved in fibrosis, inflammation and consequent tissue remodeling
- Elevated baseline plasma galectin-3 levels, implicating adverse pathophysiology, have clinically been shown to be associated with significantly increased heart failure mortality and morbidity
- An FDA-approved assay for galectin-3 has recently become available.
- Recent experimental studies suggested a role for galectin-3 in the kidney's response to injury:



Modified Citrus Pectin Reduces Galectin-3 Expression and Disease Severity in Experimental Acute Kidney Injury

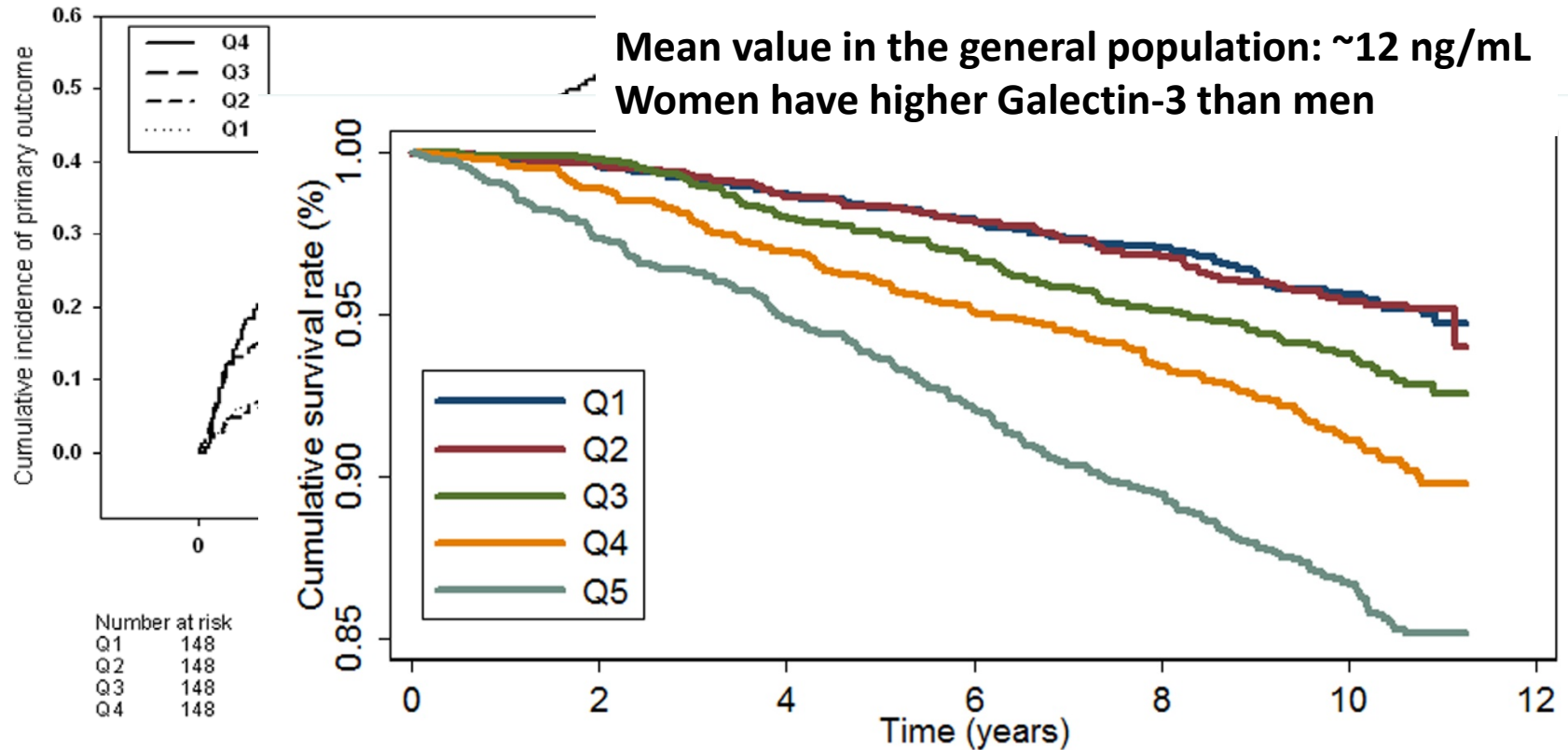
Maria Kolatsi-Joannou, Karen L. Price, Paul J. Winyard, David A. Long*

Nephro-Urology Unit, UCL Institute of Child Health, London, United Kingdom



Kolatsi-Joannou et al. *Plos One* 2011;6(4): e18683.

Galectin-3 as a biomarker



de Boer RA et al. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. *Ann Med* 2011;43:60-8.

de Boer RA et al. The fibrosis marker galectin-3 and outcome in the general population: data from PREVEND. *J Intern Med* 2011 Oct 25 doi: 10.1111/j.1365-2796.2011.02476.x.

Hypothesis and Aims

- We hypothesized that plasma galectin-3 would predict worse outcome in a population of patients with renal disease
- Aims:
 - To measure plasma galectin-3 in a well-described cohort of patients with end-stage renal disease (ESRD)
 - To relate plasma galectin-3 levels to common outcome measures in this high risk population



German Diabetes and Dialysis Study (4D)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis

Christoph Wanner, M.D., Vera Krane, M.D., Winfried März, M.D.,
Manfred Olschewski, M.Sc., Johannes F.E. Mann, M.D., Günther Ruf, M.D.,
and Eberhard Ritz, M.D., for the German Diabetes and Dialysis Study Investigators*

- Current substudy: 1168 subjects (of whom plasma was available)
- An FDA-approved assay for galectin-3 has recently become available
- During a median follow-up of 4 years, 617 patients died (49%).
- By Cox regression analysis, we assessed the association of galectin-3 with the development of all cause mortality, death due to infection, sudden cardiac death, death due to heart failure, cardiovascular (CV) events, myocardial infarction, and stroke.
- The analyses were adjusted for known predictors of adverse CV outcome including age, gender, smoking status, systolic blood pressure, BMI, LDL and HDL cholesterol and atorvastatin treatment.



Results



Characteristic	Q1	Q2	Q3	Q4
Galectin-3 (ng/mL) !	<40.48	≥40.48<51.87	≥51.87<64.20	>64.20
N	292	292	292	292
Age (years)	65 ± 8	67 ± 8	65 ± 9	65 ± 8
Gender (% men)	63	56	48	51
Atorvastatin	47	50	46	53
(ex) smoker (%)	40	40	42	39
Time on dialysis (months)	8 ± 6	8 ± 7	8 ± 7	9 ± 7
Duration of diabetes (years)	19 ± 9	18 ± 8	17 ± 9	18 ± 8
SBP (mm Hg)	144 ± 21	147 ± 23	149 ± 22	144 ± 22
DBP (mm Hg)	77 ± 11	76 ± 11	75 ± 11	75 ± 11
BMI (kg/m ²)	27.0 ± 4.5	27.4 ± 4.9	27.9 ± 4.9	27.6 ± 4.9
CAD (%)	29	29	30	31
CHF (%)	31	39	36	37
PVD (%)	43	46	43	48
Hypertension (%)	88	89	90	89
LVH (%)	12	13	11	14
Arrhythmia (%)	18	14	20	21
Ultrafiltration volume (kg)	2.1 ± 1.2	2.2 ± 1.2	2.3 ± 1.2	2.5 ± 1.2



Characteristic	Q1	Q2	Q3	Q4
Galectin-3 (ng/mL)	<40.48	≥40.48<51.87	≥51.87<64.20	>64.20
N	292	292	292	292
Age (years)	65 ± 8	67 ± 8	65 ± 9	65 ± 8
Gender (% men)	63	56	48	51
Atorvastatin	47	50	46	53
(ex) smoker (%)	40	40	42	39
Time on dialysis (months)	8 ± 6	8 ± 7	8 ± 7	9 ± 7
Duration of diabetes (years)	19 ± 9	18 ± 8	17 ± 9	18 ± 8
SBP (mm Hg)	144 ± 21	147 ± 23	149 ± 22	144 ± 22
DBP (mm Hg)	77 ± 11	76 ± 11	75 ± 11	75 ± 11
BMI (kg/m ²)	27.0 ± 4.5	27.4 ± 4.9	27.9 ± 4.9	27.6 ± 4.9
CAD (%)	29	29	30	31
CHF (%)	31	39	36	37
PVD (%)	43	46	43	48
Hypertension (%)	88	89	90	89
LVH (%)	12	13	11	14
Arrhythmia (%)	18	14	20	21
Ultrafiltration volume (kg)	2.1 ± 1.2	2.2 ± 1.2	2.3 ± 1.2	2.5 ± 1.2



Analyte	Q1	Q2	Q3	Q4
Albumin (gr/dL)	3.9 ± 0.3	3.8 ± 0.3	3.8 ± 0.3	3.8 ± 0.3
C-reactive protein (mg/L)	4.4 (1.7-8.4)	4.0 (2.0-9.7)	5.2 (2.9-13.4)	7.1 (2.9-16.0)
Total Cholesterol (mg/dL)	216 ± 44	220 ± 41	223 ± 41	221 ± 42
LDL (mg/dL)	124 ± 29	128 ± 30	126 ± 31	126 ± 28
HDL (mg/dL)	37 ± 13	37 ± 14	36 ± 13	35 ± 14
Triglycerides (mg/dL)	251 ± 161	254 ± 172	275 ± 173	269 ± 154
Hemoglobin (g/dL)	11.1 ± 1.4	10.9 ± 1.3	10.8 ± 1.3	10.7 ± 1.4
HbA1C (%)	6.8 ± 1.2	6.7 ± 1.2	6.7 ± 1.3	6.7 ± 1.3
Potassium (mmol/L)	4.9 ± 0.8	5.1 ± 0.7	5.2 ± 0.8	5.4 ± 0.9
Calcium (mmol/L)	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.3
Phosphate (mmol/L)	5.6 ± 1.3	5.9 ± 1.6	6.3 ± 1.6	6.4 ± 1.8
NT-pro-BNP (pg/mL)	2721 (1049-6848)	3190 (1169-8754)	3029 (1419-8843)	4993 (2304-13515)

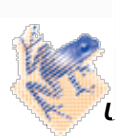
Analyte	Q1	Q2	Q3	Q4
Albumin (gr/dL)	3.9 ± 0.3	3.8 ± 0.3	3.8 ± 0.3	3.8 ± 0.3
C-reactive protein (mg/L)	4.4 (1.7-8.4)	4.0 (2.0-9.7)	5.2 (2.9-13.4)	7.1 (2.9-16.0)
Total Cholesterol (mg/dL)	216 ± 44	220 ± 41	223 ± 41	221 ± 42
LDL (mg/dL)	124 ± 29	128 ± 30	126 ± 31	126 ± 28
HDL (mg/dL)	37 ± 13	37 ± 14	36 ± 13	35 ± 14
Triglycerides (mg/dL)	251 ± 161	254 ± 172	275 ± 173	269 ± 154
Hemoglobin (g/dL)	11.1 ± 1.4	10.9 ± 1.3	10.8 ± 1.3	10.7 ± 1.4
HbA1C (%)	6.8 ± 1.2	6.7 ± 1.2	6.7 ± 1.3	6.7 ± 1.3
Potassium (mmol/L)	4.9 ± 0.8	5.1 ± 0.7	5.2 ± 0.8	5.4 ± 0.9
Calcium (mmol/L)	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.3
Phosphate (mmol/L)	5.6 ± 1.3	5.9 ± 1.6	6.3 ± 1.6	6.4 ± 1.8
NT-pro-BNP (pg/mL)	2721 (1049-6848)	3190 (1169-8754)	3029 (1419-8843)	4993 (2304-13515)

	Q1	Q2	Q3	Q4
Galectin-3 ng/mL	<40.48	≥40.48<51.87	≥51.87<64.20	>64.20

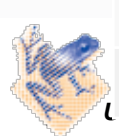
Model 1: Age and sex adjusted

Model 2: Additional adjustments for smoking, SBP, BMI, LDL/HDL, atorvastatin

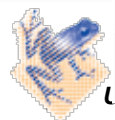
Adj. ¹ HR (95% CI)		1.04 (0.79-1.37), p=0.79	1.18 (0.90-1.54), p=0.23	1.33 (1.02-1.73), p=0.04
Adj. ² HR (95% CI)	1	1.06 (0.80-1.40), p=0.68	1.19 (0.91-1.57), p=0.21	1.38 (1.05-1.81), p=0.02
Sudden death				
Crude HR (95% CI)	1	0.71 (0.44-1.14), p=0.16	1.00 (0.65-1.54), p=0.99	1.02 (0.65-1.58), p=0.94
Adj. ¹ HR (95% CI)	1	0.68 (0.43-1.10), p=0.19	0.97 (0.63-1.50), p=0.90	1.01 (0.65-1.57), p=0.98
Adj. ² HR (95% CI)	1	0.71 (0.44-1.14), p=0.16	0.99 (0.64-1.53), p=0.99	1.04 (0.67-1.63), p=0.85
Stroke				
Crude HR (95% CI)	1	1.07 (0.57-2.01), p=0.83	1.44 (0.80-2.58), p=0.23	1.81 (1.02-3.20), p=0.04
Adj. ¹ HR (95% CI)	1	1.01 (0.54-1.90), p=0.97	1.32 (0.73-2.39), p=0.35	1.70 (0.96-3.02), p=0.07
Adj. ² HR (95% CI)	1	0.97 (0.51-1.83), p=0.93	1.32 (0.73-2.38), p=0.36	1.64 (0.92-2.93), p=0.09
Myocardial infarction				
Crude HR (95% CI)	1	1.58 (1.04-2.41), p=0.03	1.21 (0.78-1.88), p=0.40	1.61 (1.05-2.47), p=0.03
Adj. ¹ HR (95% CI)	1	1.56 (1.02-2.38), p=0.04	1.21 (0.78-1.90), p=0.39	1.61 (1.05-2.48), p=0.03
Adj. ² HR (95% CI)	1	1.58 (1.03-2.41), p=0.04	1.20 (0.77-1.88), p=0.43	1.66 (1.08-2.56), p=0.02



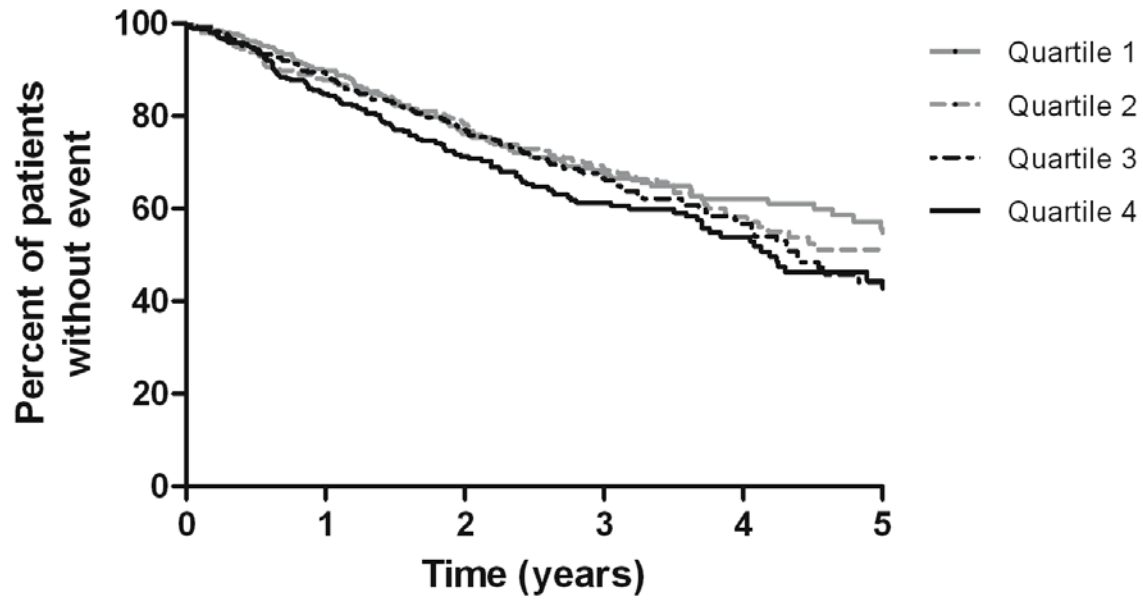
	Q1	Q2	Q3	Q4
Galectin-3 ng/mL	<40.48	≥40.48<51.87	≥51.87<64.20	>64.20
Cardiovascular events				
Crude HR (95% CI)	1	1.07 (0.81-1.41), p=0.62	1.19 (0.91-1.56), p=0.21	1.34 (1.03-1.75), p=0.03
Adj. ¹ HR (95% CI)	1	1.04 (0.79-1.37), p=0.79	1.18 (0.90-1.54), p=0.23	1.33 (1.02-1.75), p=0.04
Adj. ² HR (95% CI)	1	1.06 (0.80-1.40), p=0.68	1.19 (0.91-1.57), p=0.21	1.38 (1.05-1.81), p=0.02
Sudden death				
Crude HR (95% CI)	1	0.71 (0.44-1.14), p=0.16	1.00 (0.65-1.54), p=0.99	1.02 (0.65-1.58), p=0.94
Adj. ¹ HR (95% CI)	1	0.68 (0.43-1.10), p=0.19	0.97 (0.63-1.50), p=0.90	1.01 (0.65-1.57), p=0.98
Adj. ² HR (95% CI)	1	0.71 (0.44-1.14), p=0.16	0.99 (0.64-1.53), p=0.99	1.04 (0.67-1.63), p=0.85
Stroke				
Crude HR (95% CI)	1	1.07 (0.57-2.01), p=0.83	1.44 (0.80-2.58), p=0.23	1.81 (1.02-3.20), p=0.04
Adj. ¹ HR (95% CI)	1	1.01 (0.54-1.90), p=0.97	1.32 (0.73-2.39), p=0.35	1.70 (0.96-3.02), p=0.07
Adj. ² HR (95% CI)	1	0.97 (0.51-1.83), p=0.93	1.32 (0.73-2.38), p=0.36	1.64 (0.92-2.93), p=0.09
Myocardial infarction				
Crude HR (95% CI)	1	1.58 (1.04-2.41), p=0.03	1.21 (0.78-1.88), p=0.40	1.61 (1.05-2.47), p=0.03
Adj. ¹ HR (95% CI)	1	1.56 (1.02-2.38), p=0.04	1.21 (0.78-1.90), p=0.39	1.61 (1.05-2.48), p=0.03
Adj. ² HR (95% CI)	1	1.58 (1.03-2.41), p=0.04	1.20 (0.77-1.88), p=0.43	1.66 (1.08-2.56), p=0.02



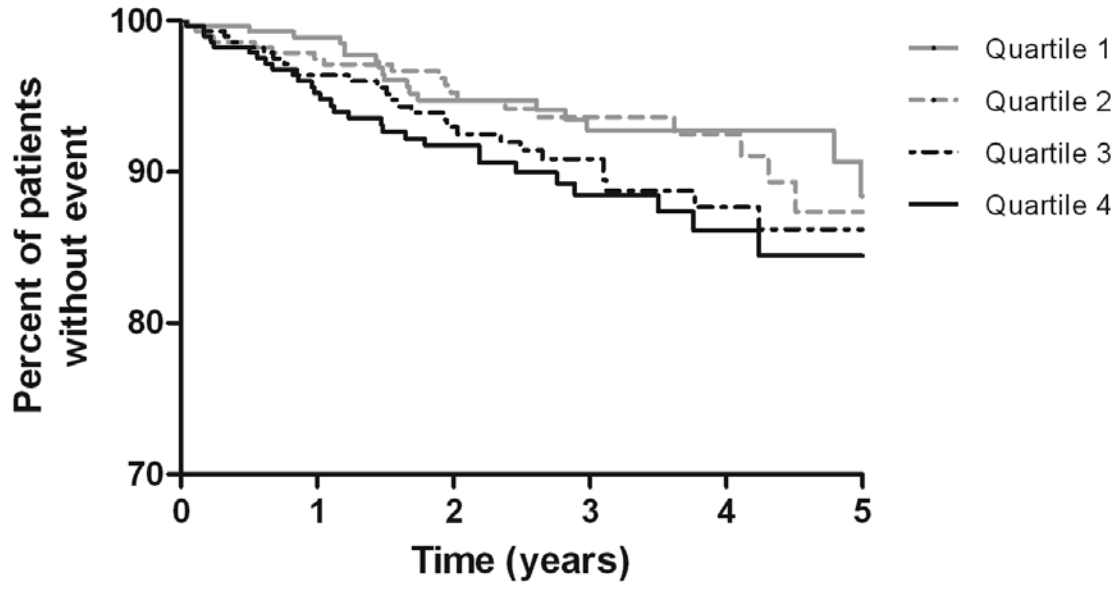
	Q1	Q2	Q3	Q4
Galectin-3 ng/mL	<40.48	≥40.48<51.87	≥51.87<64.20	>64.20
Death due to heart failure				
Crude HR (95% CI)	1	0.76 (0.26-2.20), p=0.61	1.62 (0.67-3.91), p=0.28	1.50 (0.60-3.73), p=0.39
Adj. ¹ HR (95% CI)	1	0.74 (0.26-2.13), p=0.58	1.86 (0.77-4.52), p=0.17	1.67 (0.67-4.18), p=0.27
Adj. ² HR (95% CI)	1	0.77 (0.27-2.22), p=0.63	1.79 (0.73-4.38), p=0.20	1.78 (0.71-4.47), p=0.22
Death due to infection				
Crude HR (95% CI)	1	1.35 (0.78-2.35), p=0.29	1.39 (0.81-2.40), p=0.24	1.89 (1.11-3.20), p=0.02
Adj. ¹ HR (95% CI)	1	1.30 (0.75-2.27), p=0.35	1.46 (0.84-2.52), p=0.18	1.97 (1.16-3.34), p=0.01
Adj. ² HR (95% CI)	1	1.29 (0.74-2.26), p=0.37	1.39 (0.80-2.42), p=0.24	1.96 (1.15-3.34), p=0.01
All-cause mortality				
Crude HR (95% CI)	1	1.02 (0.80-1.30), p=0.87	1.06 (0.84-1.34), p=0.61	1.32 (1.05-1.66), p=0.02
Adj. ¹ HR (95% CI)	1	0.97 (0.77-1.24), p=0.83	1.08 (0.86-1.37), p=0.50	1.36 (1.08-1.71), p=0.01
Adj. ² HR (95% CI)	1	0.99 (0.78-1.25), p=0.91	1.07 (0.84-1.36), p=0.58	1.39 (1.10-1.75), p=0.01



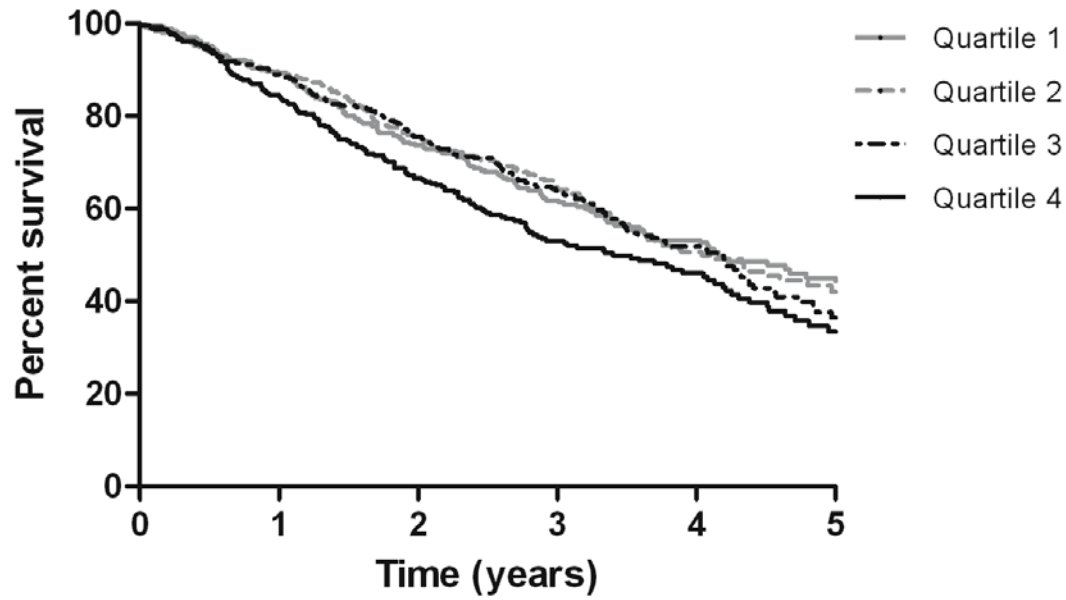
Cardiovascular events



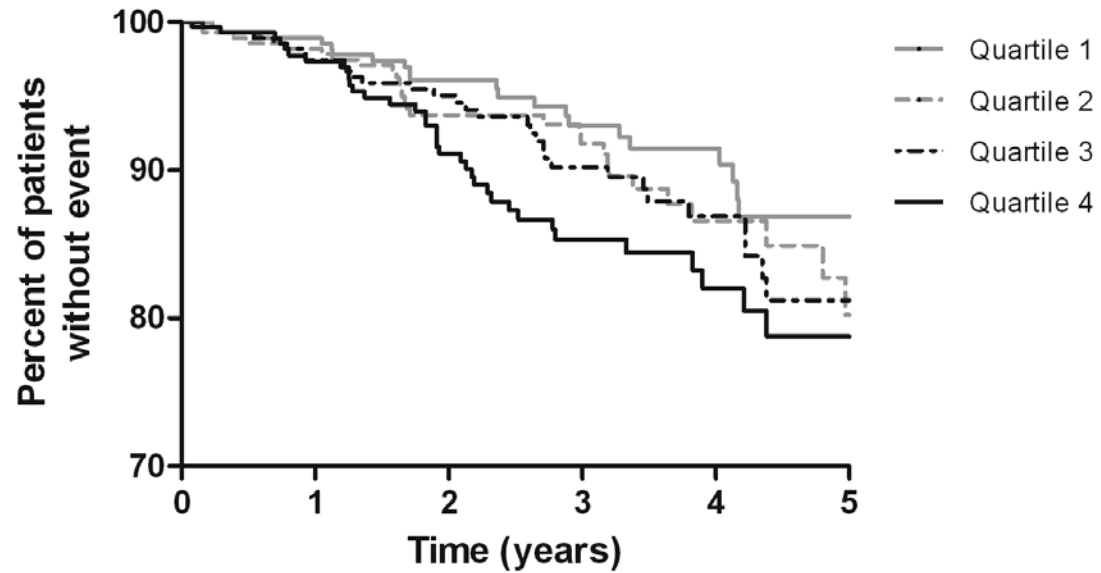
Stroke



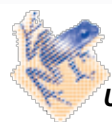
Mortality



Death due to infection



	Q1	Q2	Q3	Q4
Galectin-3 ng/mL	<40.48	≥40.48<51.87	≥51.87<64.20	>64.20
Death due to infection				
Crude HR (95% CI)	1	1.35 (0.78-2.35), p=0.29	1.39 (0.81-2.40), p=0.24	1.89 (1.11-3.20), p=0.02
Adj. ¹ HR (95% CI)	1	1.30 (0.75-2.27), p=0.35	1.46 (0.84-2.52), p=0.18	1.97 (1.16-3.34), p=0.01
Adj. ² HR (95% CI)	1	1.29 (0.74-2.26), p=0.37	1.39 (0.80-2.42), p=0.24	1.96 (1.15-3.34), p=0.01
Death due to infection				
MALES				
no. of events:	19	17	11	21
Crude HR (95% CI)	1	0.97 (0.51-1.87), p=0.93	0.74 (0.35-1.56), p=0.43	1.53 (0.82-2.84), p=0.18
Adj. ¹ HR (95% CI)	1	0.93 (0.48-1.79), p=0.83	0.76 (0.36-1.60), p=0.47	1.50 (0.81-2.79), p=0.20
Adj. ² HR (95% CI)	1	0.92 (0.47-1.77), p=0.79	0.72 (0.34-1.52), p=0.39	1.52 (0.81-2.84), p=0.19
FEMALES				
no. of events	3	12	20	16
Crude HR (95% CI)	1	3.73 (1.05-13.22), p=0.04	4.78 (1.42-16.08), p=0.01	4.64 (1.35-15.93), p=0.02
Adj. ¹ HR (95% CI)	1	3.62 (1.02-12.84), p=0.05	4.92 (1.46-16.56), p=0.01	5.05 (1.47-17.38), p=0.01
Adj. ² HR (95% CI)	1	3.69 (1.03-13.19), p=0.04	4.79 (1.41-16.28), p=0.01	5.13 (1.47-17.92), p=0.01



Conclusions

- Galectin-3 levels are extremely elevated in patients with ESRD on hemodialysis.
- High galectin-3 is independently associated with stroke, CV events, all-cause and infectious mortality in dialysis patients.
 - There seems to exist a gender interaction: women have higher levels of galectin-3 and this relates to adverse outcome
- The precise role of galectin-3 in the pathophysiology of renal disease, and the usefulness of galectin-3 as a biomarker in renal disease warrants further study.



Thank you

- **Acknowledgements:**
- Martin Dokter

