

GALECTIN-3 AND PIINP ARE ASSOCIATED WITH CARDIOVASCULAR OUTCOMES IN PATIENTS WITH HEART FAILURE, LEFT VENTRICULAR DYSFUNCTION AND DYSSYNCHRONY. INSIGHTS FROM THE CARE-HF (CARDIAC RESYNCHRONIZATION IN HEART FAILURE) TRIAL

Rossignol P^{*,†,‡,§}, Iraqi W^{*,†,‡,§}, Lopez-Andrés NS[†], Fay R^{*,†,‡}, Nuée J^{*,†,‡,§}, Ghio S^{**}, Cleland J^{**}, Lacolley P^{*,†,‡,§}, Zannad F^{*,†,‡,§}

^{*} CHU de Nancy, Department of Cardiology, Heart Failure and Hypertension Unit, Institut Lorrain du Cœur et des Vaisseaux Louis Mathieu, Vandoeuvre-Lès Nancy, France; [†] Inserm, Centre d'Investigation Clinique de Nancy CIC-P 9501, Vandoeuvre-lès-Nancy, France; [‡] Nancy-Université, Faculté de Médecine, Vandoeuvre-lès-Nancy, France; [§] Inserm U961, Nancy Université, Nancy, France; ^{**} Department of Cardiology, University of Hull, Kingston upon Hull, UK

BACKGROUND AND AIMS

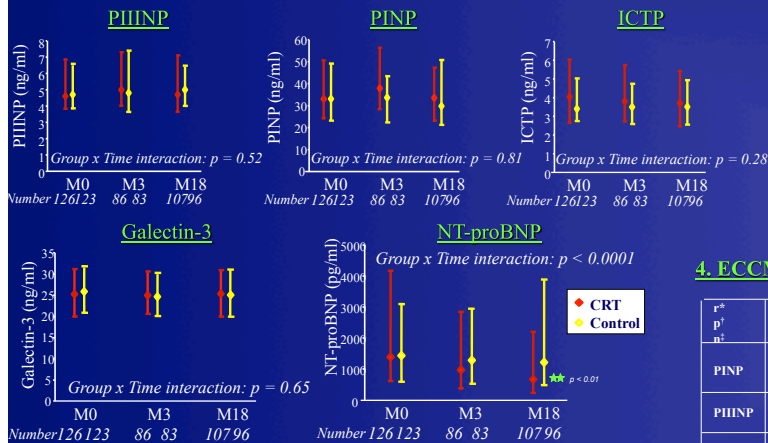
Circulating biomarkers of collagen turnover reflect cardiac extracellular matrix remodelling. The extent to which the success of cardiac resynchronisation therapy (CRT) is influenced by the degree of cardiac fibrosis and whether CRT can influence matrix remodeling has not been studied yet. The present study has been designed to determine, in patients with heart failure (HF) and cardiac dyssynchrony, whether fibrosis biomarkers are influenced by CRT and predict cardiovascular outcomes and response to CRT.

METHODS

Serum levels of fibrosis biomarkers (Gal-3, PINP, PIINP, ICTP) and of NT-proBNP were measured in 260 patients, in a substudy of CARE-HF, a randomised controlled trial which evaluated the effects of CRT, in patients with left ventricular systolic dysfunction and cardiac dyssynchrony.

RESULTS

1. Kinetics of biomarkers serum levels during the 18-month follow-up



3. Patients outcomes

Outcome	Medical therapy alone (n=128)	Medical therapy + CRT (n=132)	Chi-Square p
All-cause death	33/128 (26)	21/132 (16)	Not done
Death or hospitalisation for worsening of HF at month 18	42/120 (35)	31/129 (24)	0.057
Death or LVEF \leq 35% at month 18	103/117 (88)	72/108 (67)	0.0001
Death or NT-proBNP \geq 1000 pg/ml at month 18	77/126 (61)	60/132 (45)	0.012

6. Association between biomarkers using a composite covariable for galectin-3 and LVESV at baseline and the outcome "death or hospitalisation for worsening of HF at month 18"

Events / patients	eGFR excluded 72 / 236		eGFR included 69 / 229	
	OR * (95%CI)	p	OR (95%CI)	p
Covariable	0.54 (0.29 – 0.97)	0.041	-	NS
CRT group	-	-	-	NS
PIINP, per μ g/l	1.06 (1.00 – 1.13)	0.049	-	NS
NT-proBNP, per 1000 ng/ml	1.09 (1.01 – 1.18)	0.028	-	NS
Gal-3 \geq 30 μ g/l and/or LVESV $>$ 200 ml	2.17 (1.08 – 4.36)	0.029	2.49 (1.27 – 4.89)	0.008
eGFR per 10 ml/min/1.73m ²	-	-	0.83 (0.72 – 0.96)	0.012

4. ECCM biomarkers and risk factors correlations at baseline

r*	PIINP	PIINP	ICTP	NT-ProBNP	Gal-3	eGFR	QRS	LVEF
PINP	1.00	0.10	0.28	0.15	0.11	-0.04	-0.01	0.02
	246	246	246	245	219	239	241	220
	0.10	1.00	0.26	0.21	0.02	-0.15	0.03	-0.05
	0.14	246	<0.001	0.0009	0.72	0.017	0.63	0.45
	246	249	249	248	220	242	244	223
	0.28	0.26	1.00	0.36	0.27	-0.45	-0.05	-0.03
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.44	0.64
	246	249	249	248	220	242	244	223
	0.15	0.21	0.36	1.00	0.25	-0.30	0.13	-0.40
	0.0213	0.0009	<0.0001	<0.0001	<0.0001	0.0007	<0.0001	<0.0001
	245	248	248	732	244	712	718	672
	0.11	0.02	0.27	0.25	1.00	-0.40	-0.02	0.03
	0.12	0.72	<0.0001	<0.0001	<0.0001	<0.0001	0.79	0.62
	219	220	220	244	246	238	239	223
	-0.04	-0.15	-0.45	-0.30	-0.40	1.00	0.01	-0.07
	0.49	0.017	<0.0001	<0.0001	<0.0001	<0.0001	0.86	0.07
	239	242	242	712	738	788	773	725
	-0.01	0.03	-0.05	0.13	-0.02	0.01	1.00	-0.19
	0.92	0.63	0.44	0.0007	0.79	0.86	0.77	<0.0001
	241	244	244	718	739	773	795	733
	0.02	-0.05	-0.03	-0.40	0.03	-0.07	-0.19	1.00
	0.81	0.45	0.64	<0.0001	0.62	0.067	<0.0001	<0.0001
	220	223	223	672	223	725	733	747

5. Association between biomarkers at baseline and the outcome "death or hospitalisation for worsening of HF at month 18"

Events / patients	eGFR excluded 51 / 194		eGFR included 48 / 188	
	OR* (95%CI)	p	OR (95%CI)	p
Covariable	2.98 (1.43 – 6.22)	0.004	-	NS**
Galectin-3 $>$ 30 μ g/l	3.42 (1.65 – 7.10)	0.001	3.25 (1.55 – 6.81)	0.002
LVESV $>$ 200 ml	-	-	0.79 (0.67 – 0.94)	0.008
eGFR per 10 ml/min/1.73m ²	-	-	-	-

2. Baseline characteristics in patients with available biomarkers

	Medical therapy alone	Medical therapy plus Cardiac Resynchronisation Therapy*
Age (years)	128 67 (59-72)	132 66 (59-71)
Male gender	128 96 (75%)	132 90 (68%)
NYHA class IV	128 8 (6%)	132 6 (5%)
Primary cause of heart failure:		
Dilated cardiomyopathy	60 (47%)	58 (44%)
Ischemic heart disease	48 (38%)	53 (40%)
Heart disease of other causes	20 (16%)	21 (16%)
Heart rate (bpm)	125 70 (61-77)	130 69 (59-81)
Systolic blood pressure (mmHg)	127 115 (108-130)	131 120 (105-130)
Diastolic blood pressure (mmHg)	127 70 (60-80)	131 70 (64-80)
Left ventricular ejection fraction (%)	118 26 (22-29)	115 25 (21-29)
Left ventricular end-systolic volume (ml)	118 220 (172 – 278)	115 206 (174 – 272)
Left ventricular end-systolic volume index (ml/m ²)	118 113 (85-141)	115 108 (87-140)
QRS duration (ms)	125 160 (154-180)	130 160 (152-180)
Mitral-regurgitation area (cm ²)	97 5 (2-10)	106 5 (3-10)
TAPSE (cm)	108 1.87 (1.63 – 2.22)	105 1.98 (1.64 – 2.22)
Estimated Glomerular filtration rate (ml/min/1.72m ²)	122 60 (44-72)	130 60 (44-78)
Loop diuretic	128 120 (94%)	132 124 (94%)
Spironolactone	128 72 (56%)	132 73 (55%)
ACEi or ARb	128 122 (95%)	131 99%
Beta-blocker	128 94 (73%)	132 88 (67%)
Digitalis	128 55 (43%)	132 47 (36%)
Biomarkers		
PINP, ng/ml	121 33.1 (23.0-49.3)	125 33.0 (24.6-49.4)
PIINP, ng/ml	123 4.7 (3.8-6.5)	126 4.6 (3.8-6.8)
ICTP, ng/ml	123 3.4 (2.7-5.0)	126 4.1 (2.6-6.0)
Gal-3, ng/ml	110 25.7 (20.6-31.4)	112 25.1 (19.6-30.9)
NT-ProBNP, pg/ml	124 1408 (571-3074)	127 1362 (592-4119)

7. Association between biomarkers at baseline and the outcome "death or left ventricular ejection fraction \leq 35% at 18 months"

Events / patients	eGFR excluded 169 / 213		eGFR included 164 / 207	
	OR * (95%CI)	p	OR (95%CI)	p
Covariable	0.21 (0.09 – 0.45)	<0.0001	0.23 (0.11 – 0.51)	0.0003
CRT group	-	-	-	-
NT-proBNP, per 1000 ng/ml	1.24 (1.04 – 1.48)	0.015	1.40 (1.07 – 1.82)	0.014
LVESV $>$ 200 ml	2.69 (1.26 – 5.77)	0.011	2.68 (1.24 – 5.81)	0.013
eGFR per 10 ml/min/1.73m ²	-	-	-	NS

8. Association between biomarkers at baseline and the outcome "death /or NT-proBNP $>$ 1000 ng/l at 18 months"

Events / patients	eGFR excluded 134 / 249		eGFR included 130 / 242	
	OR * (95%CI)	p	OR (95%CI)	p
Covariable	0.32 (0.16 – 0.65)	0.002	0.33 (0.16 – 0.69)	0.0003
CRT group	-	-	-	-
Gender male	3.79 (1.59 – 9.03)	0.003	4.71 (1.88 – 11.79)	0.0009
NT-proBNP, per log eGFR per 10 ml/min/1.73m ²	5.77 (3.72 – 8.95)	<0.0001	5.14 (3.28 – 8.03)	<0.0001
eGFR per 10 ml/min/1.73m ²	-	-	0.74 (0.61-0.89)	0.0002

CONCLUSION

Increased Gal-3 and PIINP are associated with adverse long term cardiovascular outcomes but do not predict response to CRT. CRT does not favourably affect serum concentrations of markers of fibrosis markers, suggesting that CRT has little effect on the extra-cellular matrix.