Scientific letter

Trefoil factor-3 and galectin-4 as new candidates for prognostic biomarkers in ST-segment elevation myocardial infarction

Factor trefoil-3 y galectina-4 como nuevos candidatos para biomarcadores pronósticos en infarto de miocardio con elevación del segmento ST

To the Editor,

Multiple long-term prognostic clinical and procedural factors and several prognostic biomarker factors have been identified in ST-segment elevation myocardial infarction. However, current risk prediction models derived from these factors only provide a rough estimate of individual risk and more efforts are required to improve prognosis prediction.

A technique based on proximity extension assays allows analysis of a large number of cardiovascular and inflammation-related proteins present in plasma at concentrations < 10 ng/mL at the same time.

We used, in an exploratory way, a proximity extension assay approach with the aim of identifying potential biomarkers, previously selected because of a known or potential relationship with cardiovascular or inflammation, successful reperfusion and long-term prognosis in a selected ST-segment elevation myocardial infarction cohort.

This study included consecutive patients with ST-segment elevation myocardial infarction undergoing primary angioplasty in the University Clinic Hospital in Valencia, Spain, as described elsewhere.[1] Using proximity extension assay technology, 184 proteins included in Olink's inflammation and cardiovascular diseases-III panels were analyzed. The primary endpoint was long-term all-cause mortality. Secondary endpoints were a composite of all-cause mortality and spontaneous nonfatal myocardial infarction (major adverse cardiac events [MACE]), lack of ST-segment resolution ($\geq 50\%$) at 60 minutes, and the absence of TIMI 3 flow at the end of the procedure. Clinical follow-up was terminated 5 years after the inclusion period.

Of a total of 116 patients, plasma was available from 90 patients and, after exclusion of controls, only 84 patients could be analyzed for each panel. The measures are expressed in an arbitrary unit as $\log_2$ of the concentration values because of nonnormal distribution. Peripheral and coronary samples were obtained at almost the same time and a principal components analysis was performed, showing what could be considered as biological replicates.

A univariate analysis was performed to identify biomarkers that were related to the endpoints ($P < .10$). Three models were built and sequentially applied for each endpoint and each identified biomarker including: model 1, age and sex; model 2, model 1 plus all endpoint-related variables ($P < .10$ in the univariate analysis); model 3, model 2 plus variables considered clinically relevant by the investigators (age, sex, diabetes mellitus time from symptoms to reperfusion, culprit vessel diameter, hypertension, hypercholesterolemia, smoking, troponin T, previous coronary revascularization, left ventricular ejection fraction at the time of discharge). Candidate biomarkers were excluded for the next model if the P value was $>.05$ in either of the 2 replicates.

ST-segment resolution $\geq$ 50% was achieved in 53 (63.1%) patients and TIMI 3 flow was observed in 61 (81.0%) patients. Long-term follow-up was completed at a median of 4.14 [3.73-4.49] years with an overall mortality of 9.5% (n = 8), and there were 5 (6.0%) nonfatal myocardial infarctions (MI), obtaining a MACE rate of 14.3%.

No significant differences were found related to ST-segment resolution or TIMI 3 and consequently multivariate analyses were not performed for these endpoints.

After Benjamini-Hochberg correction, 9 biomarkers were selected as candidates to be predictors for long-term mortality in model 1. Only 4 remained as significant in model 2 and galectin-4 (Gal-4) (hazard ratio [HR] 2.998; 95% confidence interval [95%CI] 1.489-5.996; $P = .002$), growth/differentiation factor 15 (GDF-15) (HR, 2.483; 95%CI, 1.072-5.753; $P = .034$) and tumor necrosis factor receptor 1 (TNFR1) (HR, 10.554; 95%CI, 2.950-37.767; $P = .0003$) in model 3 with similar values in the same analyses with the biological replicates (table 1). For MACE, all the initial candidate biomarkers remained as significant predictors in the 3 models (GDF-15, trefoil factor 3 [TFF3] and TNFR1) (table 1). Kaplan-Meier plots were generated to express graphically the association of the predictors with mortality and MACE (figure 1) and C-statistics for model 3 for mortality and MACE are shown in table 1. The cutoff values used derived from receiver operating characteristic curves (5.331 for Gal-4, 8.365 for TNFR1 and 7.727 for GDF-15 [mortality] and 6.3620 for TFF3, 8.365 for TNFR1 and 8.477 for GDF-15 [MACE]).

This study identifies 2 new potential long-term prognostic biomarkers in MI: Gal-4 for overall mortality and TFF3 for MACE. Gal-4 is a carbohydrate-binding protein belonging to the galectin family that, as far as we know, has not been related to cardiovascular diseases. However, it has been described that Gal-4 increases interleukin 6[2] secretion, which has been demonstrated to be deleterious in MI. TFF3 has been found to a be a prognostic biomarker in chronic heart failure[3] but its mechanism of action in MI is still unknown.

Skau et al.[4] performed a similar study with Olink's cardiovascular diseases-I panel, identifying GDF-15 and TRAIL-R2 as long-term prognostic biomarkers but Gal-4 and TFF3 were not studied and TRAIL-R2 was not included in either our cardiovascular diseases-III or inflammation panels.

TNFR1[5] and GDF-15[6] are 2 well-known and studied prognostic biomarkers in MI. Despite our low number of events, these biomarkers and Gal-4 and TFF3, which have been tested in a robust method intended to minimize false results, could be strong prognostic biomarker candidates in MI and larger studies should be performed.

Table 1
Multivariate analyses for mortality and MACE

Mortality	Cox1 (*P* value)		Cox2 (*P* value)		Cox3 (*P* value)		Cox 3 HR [95%CI]	
	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2
Gal-4	.016179	.004875	.002077	.00082	.002077	.005476	2.998 [1.489-5.996]	3.3378 [1.431-7.976]
GDF15	.000016	.000565	.000276	.000131	.022067	.000131	2.483 [1.072-5.753]	2.644 [1.607-4.352]
TNFR1	.000038	.000039	.000291	.000139	.000291	.000139	10.554 [2.950-37.767]	36.653 [5.747-233.735]
FABP4	.010321	.000174	.000641	.000511	NS	NS		
IGFBP2	.031316	.034437	.088723	.037646				
TFF3	.000054	.000046	NS	.000144				
TGF-α	.000241	.003828	NS	.002841				
TNFR2	.001752	.01811	NS	NS				
LTBR	.000862	.029051	NS	NS				
MACE	Cox 1 (*P* value)		Cox 2 (*P* value)		Cox 3 (*P* value)		Cox 3 HR [95%CI]	
	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2
TFF3	.001565	.000278	.001565	.000278	.017755	.002164	6.472 [1.995-21.424]	12.192 [2.913-57.233]
GDF-15	.000282	.000026	.000282	.000026	.000418	.000091	2.140 [1.398-3.277]	2.658 [1.615-4.373]
TNFR1	.001561	.000097	.0036	.000097	.000708	.000134	5.908 [2.296-15.205]	34.406 [5.890-200.961]

C-statistic	Long-term mortality	MACE
Clinical	0.770	0.730
TNFR1	0.918	0.778
GDF-15	0.832	0.717
Gal-4	0.817	NA
TFF3	NA	0.793

95%CI, 95% confidence interval; FABP4, fatty acid-binding protein 4; Gal-4, galectin-4; GDF-15, growth/differentiation factor 15; HR, hazard ratio; IGFBP2, insulin-like growth factor binding protein 2; LTBR, lymphotoxin beta receptor; MACE, major adverse cardiac events; NA, not applicable; NS, not significant; TFF3, trefoil factor 3; TGF-α, transforming growth factor-α; TNFR1, tumor necrosis factor receptor 1; TNFR2, tumor necrosis factor receptor 2.
Cox 1 model: age and sex. Cox 2 model: age, sex, diabetes mellitus time from symptoms to reperfusion and culprit vessel diameter. Cox 3 model: age, sex, diabetes mellitus time from symptoms to reperfusion, culprit vessel diameter, hypertension, hypercholesterolemia, smoking, troponin T, previous coronary revascularization, left ventricular ejection fraction at the time of discharge.
HR and 95%CI are only shown for the Cox 3 model. *P* values are shown for all the models.
Replicate 1 reflects peripheral plasma and replicate 2 coronary plasma.

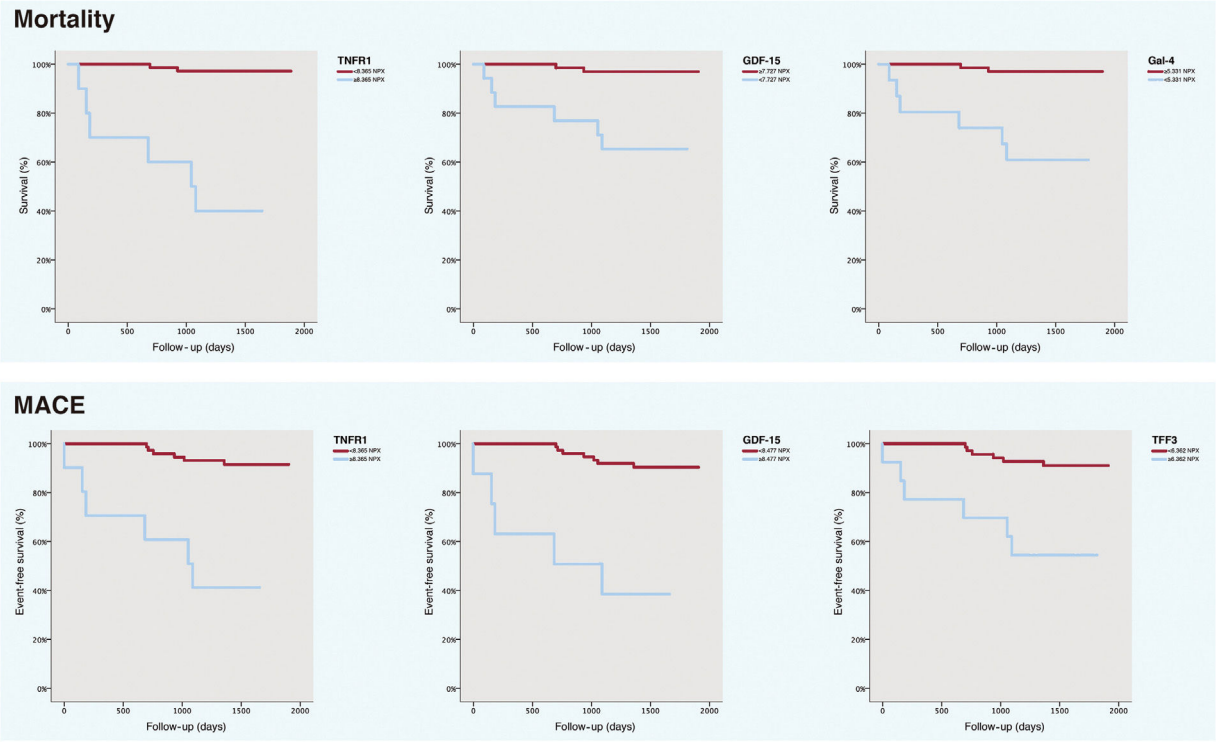

Figure 1. Candidate biomarker Kaplan-Meier curves for mortality and MACE. Gal-4, galectin-4; GDF-15, growth/differentiation factor 15; MACE, major adverse cardiac events; NPX, normalized protein expression; TNFR1, tumor necrosis factor receptor 1; TFF3, trefoil factor 3.

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CONFLICTS OF INTEREST

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Experience of percutaneous coronary intervention in the pediatric and adolescent population in a referral center for congenital heart disease

Experiencia en la intervención coronaria percutánea en población pediátrica y adolescente en un centro de referencia de cardiopatías congénitas

To the Editor,

Percutaneous coronary intervention (PCI) is a well-established treatment for adult coronary artery disease of any cause, although atherosclerotic disease in the main indication. PCI improves both symptoms and survival, especially in patients with acute myocardial infarction. The procedure, however, is much less well established in pediatric patients, in whom it is limited to isolated cases without problems of vessel size.

Atherosclerotic disease is very rare in children and has multiple causes: congenital heart defects, Kawasaki disease, graft vascular disease (GVD) in heart transplant recipients, extrinsic conduit compression causing right ventricular outflow tract obstruction, and occlusion following heart surgery with coronary manipulation such as arterial switch operation (AS) for dextro-transposition of the great arteries (d-TGA) and the Ross procedure in patients with aortic valve disease.[1,2]

In this letter, we present our experience with PCI performed in patients younger than 18 years at a high-volume center exclusively dedicated to pediatric interventions between 2005 and 2008 (table 1). In this period, 18 procedures were performed in 15 patients with 19 coronary lesions and a mean age of 7 years (range, 13 days to 17 years). Four patients were younger than 1 month and 6 weighed less than 10 kg. Ten patients had congenital heart disease: 4 had d-TGA treated with the Jatene ASO and LeCompte maneuver, 5 had congenital aortic valve disease—treated with the Ross procedure in 4 patients (figure 1) and percutaneous aortic valvuloplasty in one—and 1 had a heart anomaly treated with coronary reimplantation surgery. There were also 4 heart transplant recipients with GVD and 1 patient with Kawasaki disease and coronary and cerebral aneurysms.

Table 1
Characteristics of children and adolescents who underwent percutaneous coronary intervention

Age	7 y (range, 13 d to 17 y)
Sex	12 boys/3 girls
Weight	26.6 kg (range, 3.3-90.0 kg)
Underlying heart condition	
d-TGA	4
Congenital aortic valvulopathy (stenosis, regurgitation, or double lesion)	5
Coronary anomaly	1
Kawasaki disease	1
Heart transplant	4
Location of coronary lesion	
Left main coronary artery	4
Left anterior descending artery	4
Circumflex artery	2
Right coronary artery	9
Mechanism/cause	
Postsurgical	9
Jatene arterial switch operation	4
Early	2
Late	2
Ross procedure	4
Coronary reimplantation	1
After percutaneous aortic valvuloplasty	1
Graft vascular disease	4
Vasculitis (Kawasaki disease)	1