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Relationship between biomarkers and subsequent clinical and angiographic restenosis after paclitaxel-eluting stents for treatment of STEMI: a HORIZONS-AMI substudy

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Abstract Drug-eluting stents (DES) reduce the incidence of in-stent restenosis (ISR) after primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI). Whether the use of biomarkers might be of utility to identify patients who remain at risk for DES ISR after primary PCI has never been examined. A total of 26 biomarkers were measured at enrollment and 30 days and analyzed at a central core laboratory in 501 STEMI patients from the HORIZONS-AMI trial. All patients underwent primary PCI with the TAXUS paclitaxel-eluting stent (PES), were scheduled for routine angiographic follow-up at 13 months, and were followed for 3 years. Mean in-stent late-loss was 0.28 ± 0.57 mm, and target lesion revascularization (TLR) at 3 years occurred in 9.1 % of patients. Low levels of interleukin-6 (IL-6) and placental growth factor (PLGF) at admission were associated with both higher in-stent late loss and ischemia-driven TLR. Additionally, low admission levels of cardiotrophin-1 (CT-1) were associated with higher rates of ischemia-driven TLR. At 30-day follow-up lower values of IL-1ra (IL-1ra), matrix metalloproteinase 9 (MMP9), and myeloperoxidase (MPO), and a decline relative to admission in IL-1ra, monocyte chemotactic protein-1 (MCP-1), and MMP9 were associated with higher in-stent late loss. Low values of IL-6 at 30 days were also associated with ischemia-driven TLR. After multivariate adjustment, only MPO at 30 days and a decline of MCP-1 between admission and 30 days were associated with

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in-stent late loss, and only CT-1 was associated with TLR. MPO at 30 days and a decline of MCP-1 between admission and 30 days were independently associated with in-stent late loss, and CT-1 was associated with TLR. Additional studies to confirm and validate the utility of these biomarkers are warranted.

Keywords Biomarkers · Drug eluting stents · In-stent restenosis · Primary percutaneous coronary intervention

Introduction

By sealing dissection planes and enlarging luminal dimensions, implantation of coronary artery stents reduces the risk of early and late recurrent ischemia and reocclusion of the infarct-related artery compared to balloon angioplasty alone in patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) [1]. This reduction in restenosis has resulted in a decrease in the need for repeat coronary intervention, but did not reduce mortality or reinfarction. Compared with bare-metal stents, drug-eluting stents (DES) are associated with a further reduction in in-stent late loss and repeat revascularization with similar rates of death, reinfarction, and stent thrombosis [2]. Nonetheless, repeat revascularization is still performed in ~5–7 % of patients treated with primary PCI and DES for STEMI, and angiographic restenosis occurs in ~15–20 % of lesions [3].

Restenosis after stent implantation is caused by a multifactorial process including neointima formation, smooth muscle proliferation, and lipid oxidation [4, 5]. Thrombus may also participate in the restenotic process [6]. The use of inflammatory and thrombotic cardiac biomarkers may help to identify patients at high risk for clinical and angiographic restenosis. The identification of a subgroup of patients at high risk to develop restenosis can be important to target specific pharmacologic or alternative therapies to reduce the risk of restenosis in these patients. We therefore performed an exploratory study to determine the relationship between 26 established and novel biomarkers and restenosis in STEMI patients treated with primary PCI and DES from a pre-specified substudy of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial.

Methods

Study population and design

The design and results of the HORIZONS-AMI trial have been previously published [7–10]. Briefly, 3,602 patients with STEMI were randomized in an open-label fashion and in a 1:1 ratio to treatment with bivalirudin alone (1,800 patients) or with unfractionated heparin plus a GPI (1,02 patients). Consecutive patients ≥18 years of age who presented within 12 h after the onset of symptoms and who had ST-segment elevation of 1 mm or more in two or more contiguous leads, new left bundle-branch block, or true posterior myocardial infarction were considered for enrollment. Emergency coronary angiography with left ventriculography was performed after randomization, with subsequent triage to treatment with PCI, coronary artery bypass grafting (CABG), or medical management at physician discretion. After patency was restored in the infarct-related vessel, eligible patients were randomly assigned again, in a 3:1 ratio, to either paclitaxel-eluting stents (PES, TAXUS Express, Boston Scientific) or an uncoated, but otherwise identical BMS (Express, Boston Scientific).

Clinical and angiographic follow-up

Clinical follow-up was planned at 30 days, 6, and 12 months, and then yearly for 3 years total. Routine angiographic follow-up at 13 months was pre-specified for all patients in the biomarkers substudy, with the exception of patients in whom stent thrombosis occurred or bypass graft surgery was performed within 30 days. Patients with documented restenosis before 13 months, or with clinically driven angiography after 6 months but before 13 months, were also considered to have met the angiographic follow-up requirement. If a patient had documented restenosis before 13 month, the pre-intervention in-stent late loss measurements were used.

Biomarkers substudy

A total of 501 patients randomly assigned to receive PES in the angiographic follow-up cohort were enrolled in the

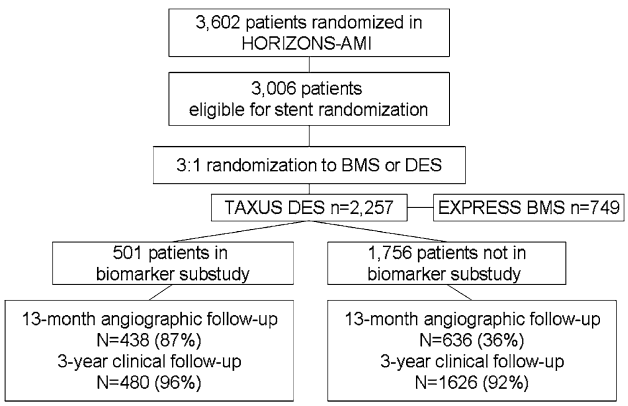

Fig. 1 Patient flow chart. *HORIZONS-AMI* harmonizing outcomes with revascularization and stents in acute myocardial infarction, *DES* drug-eluting stent, *BMS* bare metal stent

Table 1 Demographic, angiographic and procedural characteristics in patients randomized to treatment with PES according to enrollment in the biomarker substudy

Demographic characteristics	Patients in biomarker substudy ($n = 501$)	Patients not in biomarker substudy ($n = 1756$)	p Value
Age in years	60.1 (51.6–69.2)	59.8 (52.6–69.5)	0.3
Male	78.5 %	76.5 %	0.34
Diabetes	14.1 %	16.7 %	0.18
Insulin dependent diabetes mellitus	3.6 %	4.6 %	0.35
Hypertension	53.4 %	50.5 %	0.24
Hyperlipidemia	43.7 %	41.8 %	0.45
Body mass index	27.2 (24.7–30.1)	27.1 (24.5–30.1)	0.47
Current smoker	48.3 %	45.8 %	0.33
Anemia	11.0 %	11.0 %	0.98
Creatinine clearance (mL/min)	95.3 (72.6–118.6)	88.2 (67.6–112.5)	<0.01
Previous myocardial infarction	6.0 %	10.0 %	<0.01
Previous PCI	7.8 %	10.0 %	0.14
Previous coronary artery bypass graft surgery	1.6 %	2.4 %	0.29
Killip class >1	6.6 %	9.5 %	0.04
History of congestive heart failure	3.8 %	2.0 %	0.03
Angiographic and procedural characteristics			
Symptom onset to balloon (median [IQR]), hours)	3.6 (2.6–5.3)	3.7 (2.7–5.5)	0.58
LVEF <40 %	12.1 %	15.0 %	0.12
Infarct related artery (%)			0.78
Left main (%)	0.0	0.4	
Left anterior descending (%)	39.0	40.8	
Right coronary (%)	15.3	42.2	
Left circumflex (%)	45.0	15.5	
Saphenous vein graft (%)	0.7	1.0	
Right internal mammary artery graft (%)	0.0	0.1	
TIMI flow (%)			
Baseline			0.86
Grade 0 or 1	61.6	67.0	
Grade 2	15.7	16.4	
Grade 3	22.7	16.6	
Final			0.54
Grade 0 or 1	0.4	1.5	
Grade 2	4.0	7.1	
Grade 3	95.6	91.4	
Number of stents implanted (mean ± SD)	1.6 ± 0.9	1.5 ± 0.8	0.57
Total stent length (median [IQR]) (mm)	24 (20–40)	24.0 (20–36)	0.35

formal biomarker substudy. Venous blood samples were obtained at study enrollment before stent implantation, hospital discharge, 30 days and 1 year. A total of 26 inflammatory and thrombotic biomarkers were measured.

Biomarker assays

Biomarker values were determined by Alere Inc., San Diego, CA, using either Luminex or microtiter immunoassay methods. A detailed description methods and assays used is provided in the supplementary appendix.

Study endpoints and definitions

Primary endpoints of interest for the present study included in-stent late-loss and ischemia-driven target lesion revascularization (TLR). Quantitative coronary angiography was performed by an independent core laboratory

Table 2 Clinical and angiographic outcome in patients randomized to treatment with PES according to enrollment in biomarker substudy

3-Year clinical outcomes	Patients in biomarker substudy ($n = 501$) (%)	Patients not in biomarker substudy ($n = 1756$) (%)	p Value
NACE	20.2	25.7	<0.01
Major bleeding	4.8	9.5	<0.01
Major adverse cardiovascular events	17.6	20.6	0.09
Death	3.2	6.2	0.01
Myocardial infarction	5.6	7.4	0.14
Stroke	2.3	1.4	0.22
Ischemia-driven TLR	9.1	9.6	0.63
Ischemia-driven target vessel revascularization	11.1	12.9	0.24
Definite/probable stent thrombosis	3.5	5.6	0.06
13-Month angiographic outcomes	($n = 438$)	($n = 636$)	
Binary angiographic restenosis	9.0 %	9.0 %	0.99
In-stent late loss	0.28 ± 0.57	0.32 ± 0.56	0.07
In-lesion late loss	0.39 ± 0.63	0.42 ± 0.64	0.49

(Cardiovascular Research Foundation, New York, NY). Late loss was defined as the difference between minimal luminal diameter post-procedure and minimal luminal diameter at follow-up. TLR was considered to be ischemia-driven if there was stenosis of at least 50 % of the target lesion, with ischemia as documented by a positive invasive or noninvasive functional study, ischemic changes on the electrocardiogram, or symptoms referable to the target lesion, or in the absence of documented ischemia, if there was stenosis of at least 70 % as assessed by quantitative coronary analysis at the independent core laboratory.

Net adverse clinical events (NACE) was defined as the composite of major adverse cardiac events (MACE) or major bleeding not related bypass graft surgery. MACE was defined as the composite of all-cause death, reinfarction, target vessel revascularization for ischemia, or stroke. Anemia was defined using WHO criteria as a hematocrit value at initial presentation <39 % for men and <36 % for women [11]. Creatinine clearance was calculated at baseline by the Cockcroft–Gault equation [12].

Statistical analysis

Categorical variables are presented as percentages and were compared with the Fisher's exact test. Continuous variables are presented as medians with interquartile ranges, and were compared using Mann–Whitney U test. The Kaplan–Meier method was applied to estimate outcomes which were compared by log-rank test. For the purpose of the current analysis, patients were divided into tertiles according to biomarker values at admission, at 30 days, and according to differences in biomarker measurements between admission and 30 days. Associations between biomarker tertiles and in-stent late loss were investigated using the Kruskall–Wallis test. Associations between biomarker tertiles and ischemia-driven TLR were investigated using the χ^2 test, and p for trend values are given. Biomarkers that were significant in univariate analysis were included in multivariate analysis to adjust for lesion length, reference vessel diameter, and diabetes mellitus. Multivariate Cox proportional hazards was used for the endpoint of TLR, and multivariate linear regression was used for the endpoint of in-stent late loss. Stepwise methods were used to create the models with entry and exit criteria set at $p = 0.10$.

Results

Patients

Figure 1 depicts the patient flow in the biomarker substudy. Of 2,257 patients randomized to receive PES, angiographic follow-up was intended in 1,308, 501 of whom (38.3 %) were enrolled in the biomarker substudy. Table 1 shows baseline demographic, angiographic and procedural characteristics in the cohort of PES-randomized patients enrolled in versus not enrolled in the biomarker substudy. Patients in the biomarker substudy had a slightly higher creatinine clearance, lower rates of prior MI and Killip class >1, but slightly higher rates of prior congestive heart failure. Complete assessment of all pre-specified biomarkers at admission was achieved in 454 patients (91 %).

Table 2 shows the 3-year clinical and 13-month angiographic outcomes in patients randomized to treatment with

Table 3 Mean in-stent late loss at 13-month angiographic follow-up according to biomarker tertiles at admission

Biomarker	Lowest tertile Mean ± SD (mm)	Middle tertile Mean ± SD (mm)	Highest tertile Mean ± SD (mm)	*p* Value
Cytokines				
IL-1β (pg/mL)	0.25 ± 0.00	0.58 ± 0.06	4.34 ± 24.97	
In-stent late-loss (mm)	0.39 ± 0.67 (n = 196)	0.51 ± 0.75) (n = 126)	0.30 ± 0.53 (n = 135)	0.30
IL-1ra (pg/mL)	21.35 ± 4.58	35.96 ± 5.82	104.80 ± 84.89	
In-stent late-loss (mm)	0.37 ± 0.60 (n = 136)	0.43 ± 0.73 (n = 141)	0.37 ± 0.61 (n = 124)	0.98
IL-6 (pg/mL)	4.16 ± 2.14	10.99 ± 2.06	200.46 ± 1765.13	
In-stent late-loss (mm)	0.50 ± 0.74 (n = 141)	0.32 ± 0.59 (n = 132)	0.35 ± 0.59 (n = 128)	0.049
IL-8 (pg/mL)	9.34 ± 0.00	N/A	154.02 ± 484.43	
In-stent late-loss (mm)	0.41 ± 0.62 (n = 293)	N/A	0.35 ± 0.72 (n = 109)	0.45
IL-12 (pg/mL)	30.00 ± 0.00	N/A	165.61 ± 146.19	
In-stent late-loss (mm)	0.38 ± 0.64 (n = 266)	N/A	0.42 ± 0.66 (n = 140)	0.51
IL-18 (ng/mL)	0.37 ± 0.18	1.08 ± 0.25	6.30 ± 10.02	
In-stent late-loss (mm)	0.38 ± 0.59 (n = 141)	0.48 ± 0.84 (n = 126)	0.32 ± 0.48 (n = 125)	0.52
CT-1 (pg/mL)	12.11 ± 5.68	49.03 ± 17.43	372.12 ± 562.39	
In-stent late-loss (mm)	0.42 ± 0.68 (n = 139)	0.45 ± 0.75 (n = 128)	0.30 ± 0.49 (n = 136)	0.13
MCP-1 (pg/mL)	39.43 ± 11.20	64.97 ± 7.34	122.02 ± 55.43	
In-stent late-loss (mm)	0.37 ± 0.58 (n = 125)	0.40 ± 0.60 (n = 148)	0.40 ± 0.76 (n = 130)	0.72
CCL23 (ng/mL)	0.25 ± 0.07	0.43 ± 0.05	0.77 ± 0.29	
In-stent late-loss (mm)	0.38 ± 0.63 (n = 136)	0.46 ± 0.72 (n = 139)	0.32 ± 0.57 (n = 128)	0.49
Acute phase proteins				
CRP (μg/mL)	1.03 ± 0.39	2.53 ± 0.57	10.53 ± 9.25	
In-stent late-loss (mm)	0.35 ± 0.53 (n = 132)	0.42 ± 0.68 (n = 140)	0.40 ± 0.72 (n = 134)	0.52
Hormones				
BNP (pg/mL)	63.69 ± 33.24	235.74 ± 75.45	1280.21 ± 1228.74	
In-stent late-loss (mm)	0.39 ± 0.67 (n = 133)	0.37 ± 0.61 (n = 122)	0.41 ± 0.66 (n = 147)	0.86
proANP(28-151) (pg/mL)	143.34 ± 0.00	336.49 ± 40.19	1025.33 ± 1634.95	
In-stent late-loss (mm)	0.36 ± 0.58 (n = 189)	0.45 ± 0.73 (n = 80)	0.40 ± 0.69 (n = 134)	0.51
Adiponectin (ng/mL)	25654 ± 5919	42736 ± 5678	100013 ± 80555	
In-stent late-loss (mm)	0.37 ± 0.64 (n = 139)	0.37 ± 0.65 (n = 139)	0.44 ± 0.66 (n = 128)	0.39
Angiotensinogen (μg/mL)	75.31 ± 14.56	107.17 ± 7.39	165.95 ± 166.10	
In-stent late-loss (mm)	0.46 ± 0.71 (n = 126)	0.32 ± 0.54 (n = 148)	0.41 ± 0.69 (n = 132)	0.56
Renal function markers				
Cystatin-C (ng/mL)	1287.64 ± 195.27	1808.01 ± 133.93	3038.40 ± 2917.08	
In-stent late-loss (mm)	0.40 ± 0.62 (n = 123)	0.43 ± 0.71 (n = 138)	0.35 ± 0.61 (n = 145)	0.49
Matrix metalloproteinases				
MMP9 (ng/mL)	58.79 ± 21.78	136.60 ± 28.07	354.21 ± 175.85	
In-stent late-loss (mm)	0.35 ± 0.60 (n = 135)	0.39 ± 0.62 (n = 140)	0.43 ± 0.73 (n = 130)	0.37
PAPP-A (ng/mL)	1.06 ± 0.48	4.22 ± 1.44	17.06 ± 12.01	
	0.45 ± 0.71 (n = 123)	0.30 ± 0.48 (n = 141)	0.43 ± 0.73 (140)	0.78
Adhesion molecules				
ESAM (ng/mL)	24.08 ± 4.59	31.45 ± 1.66	42.50 ± 11.92	
In-stent late-loss (mm)	0.44 ± 0.71 (n = 131)	0.37 ± 0.59 (n = 139)	0.36 ± 0.65 (n = 133)	0.36
ICAM (ng/mL)	532.44 ± 110.69	913.53 ± 132.30	1707.64 ± 500.09	
In-stent late-loss (mm)	0.46 ± 0.73 (n = 135)	0.36 ± 0.59 (n = 146)	0.37 ± 0.62 (n = 125)	0.26
VCAM (ng/mL)	1049.74 ± 232.36	1733.74 ± 233.87	3699.89 ± 2511.83	
In-stent late-loss (mm)	0.35 ± 0.60 (n = 126)	0.46 ± 0.69 (n = 136)	0.36 ± 0.65 (n = 144)	0.96
Thrombotic biomarkers				
D-dimer (μg/mL)	0.16 ± 0.05	0.33 ± 0.06	1.24 ± 2.40	

Table 3 continued

Biomarker	Lowest tertileMean ± SD (mm)	Middle tertileMean ± SD (mm)	Highest tertileMean ± SD (mm)	*p* Value
In-stent late-loss (mm)	0.43 ± 0.69 ($n = 148$)	0.27 ± 0.53 ($n = 125$)	0.46 ± 0.70 ($n = 130$)	0.73
vWF (ng/mL)	93682 ± 33127	213239 ± 38062	545319 ± 295786	
In-stent late-loss (mm)	0.39 ± 0.60 ($n = 121$)	0.35 ± 0.66 ($n = 141$)	0.43 ± 0.68 ($n = 144$)	0.56
Growth factors				
PLGF (pg/mL)	13.72 ± 3.19	21.46 ± 2.39	55.49 ± 182.34	
In-stent late-loss (mm)	0.48 ± 0.69 ($n = 144$)	0.44 ± 0.73 ($n = 132$)	0.24 ± 0.46 (127)	0.0019
Vasodilators				
CGRP (pg/mL)	162.02 ± 0.00	N/A	3022.18 ± 5371.18	
In-stent late-loss (mm)	0.41 ± 0.67 ($n = 336$)	N/A	0.31 ± 0.53 ($n = 67$)	0.29
Markers of myocardial injury				
hFABP (ng/mL)	0.35 ± 0.24	1.89 ± 0.68	17.27 ± 32.63	
In-stent late-loss (mm)	0.49 ± 0.74 ($n = 145$)	0.32 ± 0.60 ($n = 134$)	0.35 ± 0.57 ($n = 124$)	0.07
MPO (ng/mL)	36.94 ± 22.35	113.62 ± 21.97	222.97 ± 61.08	
In-stent late-loss (mm)	0.36 ± 0.58 ($n = 125$)	0.39 ± 0.66 ($n = 134$)	0.42 ± 0.70 ($n = 143$)	0.41

SD standard deviation, *IL* interleukin, *CT-1* cardiotrophin-1, *MCP-1* monocyte chemotactic protein-1, *CCL23* chemokine ligand 23, *CRP* C-reactive protein, *BNP* b-type natriuretic peptide, *proANP* pro-atrial natriuretic peptide, *MMP-9* matrix metalloproteinase 9, *PAPP-A* pregnancy-associated protein A, *ESAM* endothelial cell-selective adhesion molecule *ICAM* inter-cellular adhesion molecule, *VCAM* vascular cell adhesion molecule, *vWF* von Willebrand factor, *PLGF* placental growth factor, *CGRP* calcitonin gene-related peptide, *hFABP* heart-type fatty acid binding protein, *MPO* myeloperoxidase

the PES stratified according to enrollment in the biomarker substudy. Patients in the biomarker substudy had lower rates of NACE, major bleeding and mortality at 3-year follow-up. The 3-year ischemia-driven TLR rate was similar in patients in the biomarker substudy (9.1 %) and patients not in the substudy (9.6 %, $p = 0.63$). There were also no significant differences in the rates of binary angiographic restenosis or in-stent or in-lesion late loss between both the groups at 13-month angiographic follow-up.

Relationship between biomarkers and late loss

Table 3 shows mean in-stent late loss at 13-month angiographic follow-up according to admission biomarker tertiles. Two biomarkers were identified which showed an inverse relationship with in-stent late loss. Low levels of Interleukin-6 (IL-6) and low levels of placental growth factor (PLGF) were associated with higher in-stent late loss at 13-month angiographic follow-up.

Associations between in-stent late loss and 30-day biomarker, and differences between 30-day and admission biomarkers are shown in Table 4. Lower values of Interleukin 1 receptor antagonist (IL-1ra), matrix metalloproteinase 9 (MMP9), myeloperoxidase (MPO) were associated with greater late loss. Moreover, a decline between admission and 30 days in biomarker values of IL-1ra, MMP9, and monocyte chemotactic protein-1 (MCP-1) were associated with greater late loss.

After multivariate adjustment, only MPO at 30 days and a decline of MCP-1 between admission and 30 days were independent predictors of lower in-stent late-loss (Table 7).

Relationship between biomarkers and ischemia-driven TLR

Table 5 shows 3-year ischemia-driven TLR rates according to admission biomarker tertiles. Three biomarkers showed an inverse relationship with ischemia-driven TLR. Lower levels of IL-6, PLGF and cardiotrophin-1 (CT-1) were associated with higher rates of ischemia-driven TLR at 3 years.

Table 6 shows 3-year ischemia-driven TLR rates according to 30-day biomarker tertiles and tertiles of differences between admission and 30-day biomarkers. Low values of IL-6 at 30 days were also associated with greater rates of ischemia-driven TLR.

After multivariate analysis, only CT-1 at admission was an independent predictor of a lower TLR rate at 3-year follow-up (Table 7).

Discussion

This formal biomarker substudy from the large-scale HORIZONS-AMI trial identified a number of biomarkers that were associated with angiographic and/or clinical restenosis after PES implantation in STEMI. Low levels of

Table 4 Mean in-stent late loss at 13-month angiographic follow-up according to biomarker tertiles measured at 30 days and tertiles of changes in biomarkers between admission and 30 days

Biomarker	Lowest tertile Mean ± SD (mm)	Middle tertile Mean ± SD (mm)	Highest tertile Mean ± SD (mm)	*p* Value
Cytokines				
IL-1β (pg/mL) at 30 days	0.25 ± 0.00	0.57 ± 0.05	9.18 ± 66.75	
In-stent late-loss (mm)	0.42 ± 0.74 ($n = 160$)	0.53 ± 0.65 ($n = 46$)	0.34 ± 0.50 ($n = 99$)	0.43
ΔIL-1β (pg/mL)	−1.23 ± 3.22	−0.01 ± 0.03	5.31 ± 38.89	
In-stent late-loss (mm)	0.36 ± 0.61 ($n = 94$)	0.44 ± 0.76 ($n = 104$)	0.44 ± 0.60 ($n = 99$)	0.41
IL-1ra (pg/mL) at 30 days	20.13 ± 4.43	34.72 ± 5.19	96.94 ± 79.90	
In-stent late-loss (mm)	0.60 ± 0.85 ($n = 103$)	0.41 ± 0.60 ($n = 105$)	0.20 ± 0.38 ($n = 105$)	<0.0001
ΔIL-1ra (pg/mL)	−50.03 ± 69.43	−1.43 ± 3.83	36.68 ± 63.65	
In-stent late-loss (mm)	0.56 ± 0.74 ($n = 90$)	0.42 ± 0.73 ($n = 96$)	0.29 ± 0.50 ($n = 111$)	0.005
IL-6 (pg/mL) at 30 days	3.55 ± 1.71	9.58 ± 2.22	234.81 ± 1986.95	
In-stent late-loss (mm)	0.43 ± 0.67 ($n = 106$)	0.50 ± 0.81 ($n = 98$)	0.30 ± 0.43 ($n = 93$)	0.14
ΔIL-6 (pg/mL)	−28.49 ± 72.34	−1.83 ± 2.29	19.59 ± 33.39	
In-stent late-loss (mm)	0.41 ± 0.63 ($n = 98$)	0.39 ± 0.69 ($n = 97$)	0.44 ± 0.67 ($n = 89$)	0.73
IL-8 (pg/mL) at 30 days	9.34 ± 0.00	N/A	135.23 ± 506.18	
In-stent late-loss (mm)	0.45 ± 0.67 ($n = 207$)	N/A	0.32 ± 0.62 ($n = 98$)	0.11
ΔIL-8 (pg/mL)	−11.34 ± 49.12	N/A	65.27 ± 181.68	
In-stent late-loss (mm)	0.46 ± 0.69 ($n = 223$)	N/A	0.29 ± 0.56 ($n = 74$)	0.052
IL-12 (pg/mL) at 30 days	30.00 ± 0.00	N/A	234.78 ± 268.41	
In-stent late-loss (mm)	0.39 ± 0.63 ($n = 206$)	N/A	0.45 ± 0.71 ($n = 100$)	0.44
ΔIL-12 (pg/mL)	−20.91 ± 46.03	N/A	156.50 ± 314.42	
In-stent late-loss (mm)	0.39 ± 0.62 ($n = 241$)	N/A	0.50 ± 0.81 ($n = 57$)	0.27
IL-18 (ng/mL) at 30 days	0.41 ± 0.19	1.07 ± 0.25	6.19 ± 13.67	
In-stent late-loss (mm)	0.42 ± 0.62 ($n = 103$)	0.45 ± 0.79 ($n = 103$)	0.36 ± 0.54 ($n = 99$)	0.48
ΔIL-18 (ng/mL)	−3.77 ± 8.16	0.00 ± 0.25	3.93 ± 9.65	
In-stent late-loss (mm)	0.35 ± 0.52 ($n = 98$)	0.56 ± 0.84 ($n = 99$)	0.34 ± 0.56 ($n = 99$)	0.94
CT-1 (pg/mL) at 30 days	9.48 ± 2.84	36.16 ± 11.76	288.49 ± 612.77	
In-stent late-loss (mm)	0.50 ± 0.80 ($n = 109$)	0.38 ± 0.64 ($n = 97$)	0.34 ± 0.47 ($n = 99$)	0.07
ΔCT-1 (pg/mL)	−178.35 ± 260.73	−13.24 ± 12.77	130.29 ± 302.73	
In-stent late-loss (mm)	0.40 ± 0.63 ($n = 95$)	0.46 ± 0.77 ($n = 106$)	0.38 ± 0.56 ($n = 96$)	0.78
MCP-1 (pg/mL) at 30 days	45.24 ± 8.95	67.34 ± 5.50	113.17 ± 66.71	
In-stent late-loss (mm)	0.40 ± 0.60	0.50 ± 0.77	0.33 ± 0.58	0.46
ΔMCP-1 (pg/mL)	−41.92 ± 30.27	2.09 ± 7.17	44.04 ± 37.66	
In-stent late-loss (mm)	0.59 ± 0.78	0.38 ± 0.67	0.31 ± 0.51	0.002
CCL23 (ng/mL) at 30 days	0.42 ± 0.07	0.59 ± 0.05	0.89 ± 0.18	
In-stent late-loss (mm)	0.44 ± 0.74 ($n = 101$)	0.50 ± 0.69 ($n = 103$)	0.29 ± 0.50 ($n = 101$)	0.11
ΔCCL23 (ng/mL)	−0.18 ± 0.24	0.13 ± 0.05	0.40 ± 0.16	
In-stent late-loss (mm)	0.39 ± 0.65 ($n = 98$)	0.50 ± 0.78 ($n = 94$)	0.36 ± 0.56 ($n = 105$)	0.74
Acute phase proteins				
CRP (μg/mL) at 30 days	0.65 ± 0.29	1.78 ± 0.47	7.68 ± 7.60	
In-stent late-loss (mm)	0.40 ± 0.69 ($n = 93$)	0.45 ± 0.70 ($n = 107$)	0.36 ± 0.58 ($n = 106$)	0.63
ΔCRP (μg/mL)	−8.07 ± 8.94	−0.56 ± 0.39	3.34 ± 6.78	
In-stent late-loss (mm)	0.41 ± 0.75 ($n = 90$)	0.52 ± 0.73 ($n = 105$)	0.31 ± 0.47 ($n = 103$)	0.27
Hormones				
BNP (pg/mL) at 30 days	179.68 ± 90.49	544.51 ± 164.82	2440.93 ± 1399.70	
In-stent late-loss (mm)	0.35 ± 0.69 ($n = 98$)	0.45 ± 0.55 ($n = 107$)	0.43 ± 0.73 ($n = 100$)	0.39
ΔBNP (pg/mL)	−368.28 ± 570.53	230.39 ± 110.66	1655.72 ± 1312.96	
In-stent late-loss (mm)	0.42 ± 0.70 ($n = 105$)	0.36 ± 0.54 ($n = 98($	0.47 ± 0.74 ($n = 93$)	0.68

Table 4 continued

Biomarker	Lowest tertileMean ± SD (mm)	Middle tertileMean ± SD (mm)	Highest tertileMean ± SD (mm)	*p* Value
proANP(28-151) (pg/mL) at 30 days	143.34 ± 0.00	352.14 ± 38.05	970.84 ± 1699.10	
In-stent late-loss (mm)	0.42 ± 0.71 ($n = 121$)	0.39 ± 0.64 ($n = 87$)	0.41 ± 0.62 ($n = 97$)	0.86
ΔproANP(28-151) (pg/mL)	−401.88 ± 329.10	2.86 ± 18.61	498.17 ± 593.42	
In-stent late-loss (mm)	0.44 ± 0.72 ($n = 91$)	0.38 ± 0.66 ($n = 110$)	0.43 ± 0.63 ($n = 96$)	0.96
Adiponectin (ng/mL) at 30 days	24687 ± 5635	39488 ± 5302	104953 ± 92958	
In-stent late-loss (mm)	0.30 ± 0.49 ($n = 96$)	0.53 ± 0.82 ($n = 102$)	0.39 ± 0.61 ($n = 108$)	0.34
ΔAdiponectin (ng/mL)	−41315 ± 72457	−693 ± 4554	42581 ± 80087	
In-stent late-loss (mm)	0.39 ± 0.62 ($n = 97$)	0.41 ± 0.69 ($n = 103$)	0.44 ± 0.67 ($n = 98$)	0.59
Angiotensinogen (μg/mL) at 30 days	66.92 ± 14.21	96.48 ± 7.48	130.31 ± 19.12	
In-stent late-loss (mm)	0.54 ± 0.74 ($n = 107$)	0.29 ± 0.48 ($n = 104$)	0.38 ± 0.71 ($n = 95$)	0.07
ΔAngiotensinogen (μg/mL)	−76.06 ± 187.46	−9.66 ± 9.45	28.08 ± 17.53	
In-stent late-loss (mm)	0.40 ± 0.64 ($n = 102$)	0.44 ± 0.70 ($n = 103$)	0.40 ± 0.66 ($n = 93$)	0.98
Renal function markers				
Cystatin-C (ng/mL) at 30 days	1439.96 ± 245.09	1956.22 ± 143.72	2936.39 ± 1096.46	
In-stent late-loss (mm)	0.36 ± 0.61 ($n = 100$)	0.48 ± 0.73 ($n = 104$)	0.37 ± 0.63 ($n = 102$)	0.93
ΔCystatin-C (ng/mL)	−875.91 ± 2535.31	133.17 ± 123.50	865.39 ± 714.68	
In-stent late-loss (mm)	0.44 ± 0.73 ($n = 108$)	0.34 ± 0.51 ($n = 106$)	0.47 ± 0.75 ($n = 84$)	0.86
Matrix metalloproteinases				
MMP9 (ng/mL) at 30 days	36.71 ± 11.89	81.07 ± 14.65	209.00 ± 120.41	
In-stent late-loss (mm)	0.57 ± 0.72 ($n = 110$)	0.34 ± 0.57 ($n = 102$)	0.30 ± 0.64 ($n = 93$)	0.002
ΔMMP9 (ng/mL)	−244.35 ± 168.78	−45.64 ± 23.56	66.56 ± 98.19	
In-stent late-loss (mm)	0.59 ± 0.72 ($n = 90$)	0.37 ± 0.62 ($n = 105$)	0.31 ± 0.63 ($n = 106$)	0.005
PAPP-A (ng/mL) at 30 days	0.79 ± 0.20	1.43 ± 0.17	5.36 ± 22.41	
In-stent late-loss (mm)	0.29 ± 0.49 ($n = 101$)	0.56 ± 0.81 ($n = 98$)	0.38 ± 0.62 ($n = 106$)	0.37
ΔPAPP-A (ng/mL)	−15.66 ± 13.22	−2.34 ± 1.37	3.61 ± 23.68	
In-stent late-loss (mm)	0.44 ± 0.73 ($n = 101$)	0.36 ± 0.51 ($n = 98$)	0.45 ± 0.74 ($n = 90$)	0.91
Adhesion molecules				
ESAM (ng/mL) at 30 days	25.91 ± 3.68	33.98 ± 2.32	49.10 ± 14.93	
In-stent late-loss (mm)	0.47 ± 0.78 ($n = 96$)	0.41 ± 0.60 ($n = 102$)	0.36 ± 0.59 ($n = 107$)	0.22
ΔESAM (ng/mL)	−5.24 ± 5.76	2.22 ± 1.46	12.08 ± 8.87	
In-stent late-loss (mm)	0.43 ± 0.76 ($n = 95$)	0.40 ± 0.64 ($n = 102$)	0.42 ± 0.59 ($n = 101$)	0.87
ICAM (ng/mL) at 30 days	553.59 ± 145.16	1003.02 ± 156.54	1908.90 ± 661.89	
In-stent late-loss (mm)	0.42 ± 0.70 ($n = 102$)	0.48 ± 0.68 ($n = 115$)	0.30 ± 0.57 ($n = 89$)	0.21
ΔICAM (ng/mL)	−432.17 ± 235.18	37.38 ± 92.42	587.18 ± 476.98	
In-stent late-loss (mm)	0.40 ± 0.58 ($n = 100$)	0.39 ± 0.64 ($n = 104$)	0.45 ± 0.77 ($n = 94$)	0.62
VCAM (ng/mL) at 30 days	1072.96 ± 301.49	1851.49 ± 221.67	3562.05 ± 1261.87	
In-stent late-loss (mm)	0.34 ± 0.49 ($n = 98$)	0.40 ± 0.66 ($n = 108$)	0.48 ± 0.78 ($n = 100$)	0.12
ΔVCAM (ng/mL)	−1907.20 ± 2952.16	85.68 ± 244.58	1760.02 ± 1184.89	
In-stent late-loss (mm)	0.37 ± 0.60 ($n = 102$)	0.52 ± 0.73 ($n = 98$)	0.35 ± 0.65 ($n = 98$)	0.88
Thrombotic biomarkers				
D-dimer (μg/mL) at 30 days	0.16 ± 0.05	0.35 ± 0.07	1.41 ± 1.75	
In-stent late-loss (mm)	0.34 ± 0.64 ($n = 107$)	0.45 ± 0.67 ($n = 102$)	0.44 ± 0.66 ($n = 96$)	0.24
ΔD-dimer (μg/mL)	−0.68 ± 1.59	0.00 ± 0.04	0.54 ± 1.01	
In-stent late-loss (mm)	0.44 ± 0.64 ($n = 93$)	0.36 ± 0.66 ($n = 101$)	0.45 ± 0.69 ($n = 103$)	0.9
vWF (ng/mL)	78465 ± 31983	173128 ± 26385	395792 ± 166871	
In-stent late-loss (mm)	0.49 ± 0.74 ($n = 105$)	0.40 ± 0.63 ($9n = 103$)	0.32 ± 0.59 ($n = 98$)	0.07
ΔvWF (ng/mL)	−317570 ± 282853	−39944 ± 35304	164046 ± 171266	

Table 4 continued

Biomarker	Lowest tertileMean ± SD (mm)	Middle tertileMean ± SD (mm)	Highest tertileMean ± SD (mm)	*p* Value
In-stent late-loss (mm)	0.47 ± 0.72 ($n = 105$)	0.47 ± 0.75 ($n = 102$)	0.29 ± 0.45 ($n = 91$)	0.06
Growth factors				
PLGF (pg/mL)	15.02 ± 3.52	23.31 ± 1.64	70.58 ± 313.15	
In-stent late-loss (mm)	0.47 ± 0.75 ($n = 94$)	0.35 ± 0.62 ($n = 105$)	0.41 ± 0.60 ($n = 106$)	0.58
ΔPLGF (pg/mL)	−10.26 ± 9.97	0.76 ± 1.90	25.93 ± 113.76	
In-stent late-loss (mm)	0.36 ± 0.68 ($n = 96$)	0.50 ± 0.77 ($n = 95$)	0.39 ± 0.54 ($n = 106$)	0.75
Vasodilators				
CGRP (pg/mL)	162.02 ± 0.00	N/A	3318.43 ± 5886.60	
In-stent late-loss (mm)	0.44 ± 0.67 ($n = 233$)	N/A	0.32 ± 0.61 ($n = 71$)	0.18
ΔCGRP (pg/mL)	−138.43 ± 1173.03	N/A	1640.73 ± 2867.93	
In-stent late-loss (mm)	0.43 ± 0.68 ($n = 242$)	N/A	0.34 ± 0.62 ($n = 53$)	0.33
Markers of myocardial injury				
HFABP (ng/mL)	0.23 ± 0.11	0.68 ± 0.16	8.17 ± 41.81	
In-stent late-loss (mm)	0.42 ± 0.65 ($n = 107$)	0.47 ± 0.75 ($n = 95$)	0.34 ± 0.57 ($n = 103$)	0.41
ΔhFABP (ng/mL)	−12.54 ± 16.79	−1.04 ± 0.61	4.52 ± 24.26	
In-stent late-loss (mm)	0.43 ± 0.56 ($n = 95$)	0.41 ± 0.70 ($n = 101$)	0.41 ± 0.72 ($n = 101$)	0.87
MPO (ng/mL)	10.09 ± 3.11	18.49 ± 3.50	93.56 ± 103.97	
In-stent late-loss (mm)	0.58 ± 0.76 ($n = 98$)	0.37 ± 0.64 ($n = 112$)	0.27 ± 0.51 ($n = 95$)	0.001
ΔMPO (ng/mL)	−189.77 ± 56.93	−80.85 ± 24.10	25.16 ± 72.95	
In-stent late-loss (mm)	0.49 ± 0.73 ($n = 105$)	0.36 ± 0.64 ($n = 101$)	0.39 ± 0.59 ($n = 89$)	0.26

Abbreviations as in Table 3

IL-6 and PLGF at admission were associated with both higher in-stent late loss at 13-month angiographic follow-up and higher rates of ischemia-driven TLR at 3-year follow-up. Additionally, low admission levels of CT-1 were associated with higher rates of ischemia-driven TLR. At 30-day follow-up lower values of Il-1ra, MMP9, and MPO, and a decline relative to admission in IL-1ra, MCP-1, and MMP9 were associated with higher in-stent late loss. Finally, low values of IL-6 at 30 days were associated with ischemia-driven TLR. After multivariate adjustment, only MPO at 30 days and a decline of MCP-1 between admission and 30 days were independent predictors of lower in-stent late-los, and CT-1 was the only independent predictor of lower TLR.

The cytokines IL-1ra, IL-6, CT-1, and MCP-1 have been shown to contribute to atherosclerotic plaque development and plaque destabilization in animal models [13, 14]. However, little is known about their significance in the pathology of restenosis. Interestingly, IL-6 has also been found to have atheroprotective effects. For example, systemic IL-6 deficiency in a murine model enhanced atherosclerotic plaque formation [15]. It should be noted that there was only a weak association between IL-6 on admission and in-stent late loss with a univariate *p*-value of 0.49. Thus, further investigation in other studies is warranted. After multivariate analysis, CT-1 remained an independent predictor of TLR. CT-1 is a cytokine that signals via leukaemia inhibitory factor receptor gp130-dependent pathways and was originally described to induce cardiomocyte growth and survival [16]. This is the first study to identify CT-1 as a potential marker to predict clinical restenosis and further studies are needed to confirm or disprove our findings.

PLGF, a member of the vascular endothelial growth factor family, has been shown to stimulate arterial intimal thickening and macrophage accumulation in carotid arteries of cholesterol-fed rabbits [17]. In humans, PLGF has shown potential to predict death or myocardial infarction in patients with acute coronary syndromes [18]. Previous animal studies have reported a critical role for MMP9 in cell migration and intimal growth [19, 20]. Therefore, it has been hypothesized that MMP9 might play a key contributing role to the occurrence of restenosis, a theory which was not confirmed in this present study. Finally, 30-day plasma levels of MPO, a leukocyte-derived enzyme that catalyzes the formation of a number of reactive oxidant species and is associated with atherosclerosis in animal models, were also inversely related to restenosis in the current study [21].

This is the first study investigating the potential utility of biomarkers to predict restenosis in the setting of primary

Table 5 3-Year ischemia-driven TLR rates according to biomarker tertiles measured at admission

Biomarker	Lowest tertile	Middle tertile	Highest tertile	*p* Value linear trend
Cytokines				
IL-1β (pg/mL)	0.25 ± 0.00	0.58 ± 0.06	4.28 ± 22.60	
ID-TLR	10.1 % (22/218)	19.5 % (17/87)	8.3 % (13/156)	0.74
IL-1ra (pg/mL)	21.31 ± 4.53	36.18 ± 5.77	121.08 ± 155.07	
ID-TLR	9.9 % (15/152)	14.6 % (22/152)	9.7 % (15/155)	0.95
IL-6 (pg/mL)	4.16 ± 2.12	11.05 ± 2.07	172.17 ± 1598.99	
ID-TLR	17.1 % (26/152)	8.6 % (13/151)	8.3 % (13/156)	0.02
IL-8 (pg/mL)	9.34 ± 0.00	N/A	147.45 ± 452.99	
ID-TLR	12.7 % (41/323)	N/A	8.1 % (11/136)	0.16
IL-12 (pg/mL)	30.00 ± 0.00	N/A	165.61 ± 131.53	
ID-TLR	10.3 % (33/230)	N/A	13.2 % (19/144)	0.36
IL-18 (ng/mL)	0.38 ± 0.19	1.11 ± 0.25	6.02 ± 9.15	
ID-TLR	13.2 % (20/152)	13.9 % (21/151)	7.1 % (11/156)	0.09
CT-1 (pg/mL)	11.66 ± 5.43	49.14 ± 17.58	397.35 ± 642.11	
ID-TLR	15.9 % (24/151)	10.5 % (16/153)	7.7 % (12/156)	0.03
MCP-1 (pg/mL)	39.53 ± 10.63	65.58 ± 7.33	120.46 ± 52.17	
ID-TLR	8.6 % (13/152)	15.9 % (24/151)	9.6 % (15/157)	0.80
CCL23 (ng/mL)	0.25 ± 0.07	0.43 ± 0.05	0.78 ± 0.32	
ID-TLR	13.2 % (20/152)	10.5 % (16/152)	10.3 % (16/156)	0.42
Acute phase proteins				
CRP (μg/mL)	0.98 ± 0.40	2.58 ± 0.61	10.92 ± 9.30	
ID-TLR	9.7 % (15/154)	14.4 % (22/153)	9.6 % (15/157)	0.95
Hormones				
BNP (pg/mL)	62.79 ± 34.16	236.81 ± 78.09	1446.54 ± 1341.42	
ID-TLR	11.2 % (17/152)	9.9 % (15/152)	12.8 % (20/156)	0.65
proANP (pg/mL)	143.34 ± 0.00	340.56 ± 39.72	1036.80 ± 1576.91	
ID-TLR	11.3 % (24/213)	11.8 % (11/93)	11.0 % (17/156)	0.94
Adiponectin (ng/mL)	25689 ± 6025	43092 ± 5707	93505 ± 59803	
ID-TLR	13.1 % (20/153)	7.8 % (12/154)	12.7 % (20/157)	0.94
Angiotensinogen (μg/mL)	74.86 ± 16.23	107.00 ± 7.69	162.00 ± 152.64	
ID-TLR	11.1 % (17/153)	10.4 % (16/154)	12.1 % (19/157)	0.78
Renal function markers				
Cystatin-C (ng/mL)	1265.33 ± 230.51	1804.17 ± 140.41	3004.57 ± 2800.91	
ID-TLR	7.8 % (12/154)	13.8 % (21/152)	12.0 % (19/158)	0.24
Matrix metalloproteinases				
MMP9 (ng/mL)	59.51 ± 21.31	136.91 ± 27.94	368.09 ± 205.89	
ID-TLR	11.9 % (18/151)	11.8 % (18/153)	10.3 % (16/156)	0.64
PAPP-A (ng/mL)	1.08 ± 0.49	4.20 ± 1.42	21.94 ± 20.87	
ID-TLR	13.7 % (21/153)	10.5 % (16/152)	9.6 % (15/156)	0.26
Adhesion molecules				
ESAM (ng/mL)	24.05 ± 4.21	31.26 ± 1.67	44.13 ± 12.03	
ID-TLR	11.2% (17/152)	13.2 % (20/151)	9.6 % (15/157)	0.65
ICAM (ng/mL)	525.39 ± 122.72	920.09 ± 133.05	1715.62 ± 578.04	
ID-TLR	14.3 % (22/154)	11.1 % (17/153)	8.3 % (13/157)	0.10
VCAM (ng/mL)	1062.00 ± 233.72	1728.24 ± 236.80	3587.66 ± 2552.02	
ID-TLR	8.4 % (13/154)	9.9 % (15/152)	15.2 % (24/158)	0.06
Thrombotic biomarkers				
D-dimer (μg/mL)	0.16 ± 0.05	0.33 ± 0.06	1.28 ± 2.23	

Table 5 continued

Biomarker	Lowest tertile	Middle tertile	Highest tertile	*p* Value linear trend
ID-TLR	12.3 % (19/154)	7.9 % (12/151)	13.5 % (21/156)	0.75
vWF (ng/mL)	97168 ± 35679	211468 ± 37099	551206 ± 296043	
D-TLR	7.8 % (12/153)	13.7 % (21/153)	12.0 % (19/158)	0.25
Growth factors				
PLGF (pg/mL)	13.46 ± 3.21	21.49 ± 2.34	52.43 ± 164.83	
ID-TLR	15.2 % (23/151)	12.4 % (19/153)	6.4 % (10/156)	0.02
Vasodilators				
CGRP (pg/mL)	162.02 ± 0.00	N/A	2613.72 ± 4448.83	
ID-TLR	11.8 % (45/381)	0.0 %	8.8 % (7/80)	0.43
Markers of myocardial injury				
hFABP (ng/mL)	0.33 ± 0.23	1.88 ± 0.70	14.33 ± 25.46	
ID-TLR	14.4 % (22/153)	8.6 % (13/152)	10.9 % (17/156)	0.34
MPO (ng/mL)	34.54 ± 21.87	114.22 ± 21.60	224.96 ± 63.36	
ID-TLR	9.9 % (15/152)	12.6 % (19/151)	11.5 % (18/156)	0.65

ID-TLR ischemia driven target lesion revascularization, other abbreviations as in Tables 3 and 4

PCI with DES. Interestingly, all the aforementioned biomarkers showed an inverse relationship with angiographic and/or clinical restenosis in the HORIZONS-AMI biomarker substudy, both when measured at admission and when measured at 30-day follow-up. These findings may seem counter-intuitive as higher plasma levels of inflammatory markers were not associated with clinical and/or angiographic restenosis. Studies in the BMS era have reported an association between higher plasma C-reactive protein (CRP) levels and restenosis, while prior studies in the DES era reported the absence of an association between CRP and restenosis [22, 23]. The results of the current analyses also suggest that inflammation after DES implantation may have little relationship to restenosis.

In our study, only low levels of IL-6 and PLGF at admission were associated with both higher in-stent late loss and ischemia-driven TLR. The fact that biomarkers that are predictors for late loss are not automatically predictors for TLR can be explained by the fact that not every significant stenosis also causes anginal complaints, and may therefore not be revascularized, even if there is a considerable amount of late loss.

The early detection of patients at high risk of restenosis may be clinically relevant as it may help identify patients who might benefit from targeted pharmaceutical intervention or alternative therapies to reduce restenosis. For example, a recent study has suggested that triple antiplatelet therapy with cilostazol, a phosphodiesterase III inhibitor, in addition to aspirin and a thienopyridine may result in lower rates of restenosis in patients receiving DES [24, 25].

Limitations

Several limitations of this study need to be mentioned. As we measured 26 different biomarkers and evaluated each three times (admission, 30-day, and the difference between admission and 30-day), the possibility of spurious significant results due to chance cannot be excluded. Formal statistical correction for multiple comparisons was not applied. However, we consistently found lower rates of several inflammatory biomarkers to be associated with both angiographic and clinical restenosis, whether measured at admission, 30 days, or as the difference between 30 days and admission. Second, as PES were exclusively in HORIZONS-AMI, these results don't apply to other DES, such as rapamycin-eluting stents. Third, prior studies have shown that there may be gender related differences in biomarker release during acute coronary syndromes, as only 22.5 % of patients in the biomarker substudy were women, we were not able to investigate gender differences in the current study. Finally, all patients underwent primary PCI for STEMI, and these results may therefore not be applicable to patients undergoing elective stent implantation.

Conclusions

Low values of IL-6, PLGF, and CT-1 measured at admission, IL-1ra, IL-6, MPO, and MMP9 measured at 30 days, and a decline between admission and 30 days in IL-1ra, MCP1, and MMP9 were significantly associated

Table 6 3-Year ischemia-driven TLR rates according to biomarker tertiles measured at 30 days, and tertiles of changes in biomarkers between admission and 30 days

Biomarker	Lowest tertile % (n/N)	Middle tertile % (n/N)	Highest tertile % (n/N)	*p* Value
Cytokines				
IL-1β (pg/mL) at 30 days	0.25 ± 0.00	0.57 ± 0.05	9.13 ± 63.70	
ID-ID-TLR	12.9 % (22/170)	12.5 % (6/48)	6.4 (7/110)	0.09
ΔIL-1β (pg/mL)	−1.48 ± 3.37	−0.01 ± 0.03	5.39 ± 37.90	
ID-TLR	12.4 % (13/105)	10.3 % (11/107)	10.5 % (11/105)	0.66
IL-1ra (pg/mL) at 30 days	19.75 ± 4.43	34.68 ± 5.72	104.46 ± 99.81	
ID-TLR	13.8 % (15/109)	12.0 % (13/108)	6.2 % (7/113)	0.07
ΔIL-1ra (pg/mL)	−73.59 ± 175.48	−1.21 ± 3.73	47.03 ± 94.62	
ID-TLR	12.4 % (13/105)	11.4 % (12/105)	9.2 % (10/109)	0.45
IL-6 (pg/mL) at 30 days	3.50 ± 1.70	9.74 ± 2.23	215.05 ± 1878.41	
ID-TLR	14.4 % (16/111)	13.5 % (14/104)	4.4 % (5/113)	0.02
ΔIL-6 (pg/mL)	−29.58 ± 70.85	−1.76 ± 2.22	19.75 ± 32.88	
ID-TLR	7.6 % (8/105)	13.5 % (14/104)	12.0 % (13/108)	0.31
IL-8 (pg/mL) at 30 days	9.34 ± 0.00	N/A	164.59 ± 596.78	
ID-TLR	12.8 % (28/219)	N/A	6.4 % (7/109)	0.09
ΔIL-8 (pg/mL)	−15.05 ± 54.44	N/A	89.04 ± 294.13	
ID-TLR	12.7 % (30/236)	N/A	6.2 % (5/81)	0.11
IL-12 (pg/mL) at 30 days	30.00 ± 0.00	N/A	224.53 ± 218.95	
ID-TLR	10.1 % (23/227)	N/A	11.5 % (12/104)	0.70
ΔIL-12 (pg/mL)	−16.14 ± 40.14	N/A	134.44 ± 223.70	
ID-TLR	10.7 % (27/253)	N/A	11.9 % (8/67)	0.77
IL-18 (ng/mL) at 30 days	0.42 ± 0.19	1.06 ± 0.24	6.32 ± 13.24	
ID-TLR	12.8 % (14/109)	9.2 % (10/109)	9.9 % (11/111)	0.48
ΔIL-18 (ng/mL)	−3.23 ± 6.38	0.00 ± 0.27	3.82 ± 9.31	
ID-TLR	7.6 % (8/105)	17.1 % (18/105)	8.3 % (9/108)	0.88
CT-1 (pg/mL) at 30 days	9.29 ± 2.53	35.56 ± 11.82	350.02 ± 761.49	
ID-TLR	12.7 % (14/110)	11.2 % (12/107)	8.0 % (9/112)	0.26
ΔCT-1 (pg/mL)	−190.05 ± 255.07	−13.18 ± 13.16	138.87 ± 303.03	
ID-TLR	7.6 % (8/105)	12.7 % (14/110)	12.6 % (13/103)	0.25
MCP-1 (pg/mL) at 30 days	44.62 ± 9.63	67.15 ± 5.61	109.65 ± 62.57	
ID-TLR	6.4 % (7/109)	13.0 % (14/108)	12.6 % (14/111)	0.14
ΔMCP-1 (pg/mL)	−40.94 ± 29.77	2.79 ± 7.45	41.21 ± 33.52	
ID-TLR	13.3 % (14/105)	9.5 % (10/105)	10.3 % (11/107)	0.48
CCL23 (ng/mL) at 30 days	0.41 ± 0.07	0.59 ± 0.05	0.89 ± 0.19	
ID-TLR	11.0 % (12/109)	13.8 % (15/109)	7.2 % (8/111)	0.36
ΔCCL23 (ng/mL)	−0.19 ± 0.23	0.13 ± 0.05	0.40 ± 0.17	
ID-TLR	10.5 % (11/105)	16.3 % (17/104)	6.4 % (7/109)	0.33
Acute phase proteins				
CRP (μg/mL) at 30 days	0.69 ± 0.28	1.85 ± 0.49	8.06 ± 7.70	
ID-TLR	11.0 % (12/109)	11.0 % (12/109)	9.7 % (11/113)	0.76
ΔCRP (μg/mL)	−7.75 ± 8.93	−0.56 ± 0.39	3.40 ± 6.85	
ID-TLR	10.5 % (11/105)	13.1 % (14/107)	9.3 % (10/108)	0.77
Hormones				
BNP (pg/mL) at 30 days	185.14 ± 84.52	552.82 ± 174.28	2461.15 ± 1466.43	
ID-TLR	9.3 % (10/108)	10.0 % (11/110)	12.6 % (14/111)	0.42
ΔBNP (pg/mL)	−485.02 ± 765.65	219.10 ± 110.32	1721.44 ± 1371.35	
ID-TLR	12.4 % (13/105)	6.7 % (7/105)	14.0 % (15/107)	0.70

Table 6 continued

Biomarker	Lowest tertile % (n/N)	Middle tertile % (n/N)	Highest tertile % (n/N)	*p* Value
proANP(28-151) (pg/mL) at 30 days	143.34 ± 0.00	352.35 ± 37.35	968.69 ± 1595.06	
ID-TLR	9.3 % (12/129_	15.7 % (14/89)	8.1 % (9/111)	0.82
ΔproANP(28-151) (pg/mL)	−519.25 ± 716.29	3.47 ± 17.18	501.92 ± 569.99	
ID-TLR	8.7 % (9/104)	10.5 % (11/105)	13.8 % (15/109)	0.24
Adiponectin (ng/mL) at 30 days	24922 ± 5077	40348 ± 5528	100225 ± 77899	
ID-TLR	9.2 % (10/109)	10.9 % (12/110)	11.6 % (13/112)	0.56
ΔAdiponectin (ng/mL)	−37007 ± 53569	−723 ± 4378	38372 ± 66605	
ID-TLR	9.4 % (10/106)	13.2 % (14/106)	10.2 % (11/108)	0.86
Angiotensinogen (μg/mL) at 30 days	67.69 ± 14.17	96.61 ± 7.42	137.02 ± 45.45	
ID-TLR	15.5 % (17/110)	5.5 % (6/109)	10.7 % (12/112)	0.26
ΔAngiotensinogen (μg/mL)	−75.32 ± 184.77	−10.39 ± 9.27	35.61 ± 48.34	
ID-TLR	13.3 % (14/105)	10.4 % (11/106)	9.2 % (10/109)	0.33
Renal function markers				
Cystatin-C (ng/mL) at 30 days	1431.35 ± 254.14	1966.63 ± 140.43	2972.50 ± 1078.27	
ID-TLR	5.5 % (6/110)	14.8 % (16/108)	11.5 % (13/113)	0.15
ΔCystatin-C (ng/mL)	−879.30 ± 2562.33	134.33 ± 125.72	907.95 ± 700.64	
ID-TLR	13.2 % (14/106)	10.4 % (11/106)	9.3 % (10/108)	0.36
Matrix metalloproteinases				
MMP9 (ng/mL) at 30 days	37.45 ± 11.15	81.76 ± 14.67	203.22 ± 112.60	
ID-TLR	12.8 % (14/109)	10.1 % (11/109)	9.0 % (10/111)	0.36
ΔMMP9 (ng/mL)	−258.40 ± 202.84	−44.02 ± 23.23	65.71 ± 103.06	
ID-TLR	12.4 % (13/105)	9.6 % (10/104)	11.0 % (12/109)	0.75
PAPP-A (ng/mL) at 30 days	0.79 ± 0.22	1.43 ± 0.18	5.14 ± 21.84	
ID-TLR	6.4 % (7/109)	15.6 % (17/109)	9.9 % (11/111)	0.41
ΔPAPP-A (ng/mL)	−19.08 ± 18.27	−2.30 ± 1.38	2.95 ± 21.55	
ID-TLR	10.5 % (11/105)	9.5 % (10/105)	13.0 % (14/108)	0.56
Adhesion molecules				
ESAM (ng/mL) at 30 days	25.99 ± 3.84	33.98 ± 2.29	49.79 ± 15.61	
ID-TLR	11.9 % (13/109)	8.3 % (9/109)	11.7 % (13/111)	
ΔESAM (ng/mL)	−5.73 ± 6.15	2.12 ± 1.53	11.92 ± 8.51	
ID-TLR	9.5 % (10/105)	10.6 % (11/104)	12.8 % (14/109)	0.44
ICAM (ng/mL) at 30 days	562.78 ± 147.97	1001.78 ± 148.55	1966.12 ± 756.99	
ID-TLR	12.7 % (14/110)	13.8 % (15/109)	5.4 % (6/112)	0.08
ΔICAM (ng/mL)	−476.03 ± 424.26	39.44 ± 92.58	650.24 ± 572.96	
ID-TLR	10.4 % (11/106)	15.2 % (16/105)	7.3 % (8/109)	0.47
VCAM (ng/mL) at 30 days	1095.56 ± 272.27	1845.35 ± 220.40	3473.83 ± 1171.31	
ID-TLR	9.2 % (10/109)	11.8 % (13/110)	10.7 % (12/112)	0.72
ΔVCAM (ng/mL)	−1853.58 ± 3055.81	72.03 ± 240.31	1699.90 ± 1101.22	
ID-TLR	12.3 % (13/106)	12.4 % (13/105)	8.3 % (9/109)	0.35
Thrombotic biomarkers				
D-dimer (μg/mL) at 30 days	0.16 ± 0.05	0.35 ± 0.08	1.39 ± 1.66	
ID-TLR	11.0 % (12/109)	9.3 % (10/108)	11.6 % (13/112)	0.88
ΔD-dimer (μg/mL)	−0.69 ± 1.56	0.01 ± 0.04	0.55 ± 0.99	
ID-TLR	13.3 % (14/105)	9.6 % (10/104)	10.1 % (11/109)	0.45
vWF (ng/mL) at 30 days	79878 ± 31132	172561 ± 26887	426147 ± 224007	
ID-TLR	10.0 % (11/110)	14.8 % (16/108)	7.1 % (8/113)	0.47
ΔvWF (ng/mL)	−335671 ± 291586	−38614 ± 36399	186992 ± 210038	
ID-TLR	12.4 % (13/105)	15.0 % (16/107)	5.6 % (6/108)	0.11

Table 6 continued

Biomarker	Lowest tertile % (n/N)	Middle tertile % (n/N)	Highest tertile % (n/N)	*p* Value
Growth factors				
PLGF (pg/mL) at 30 days	14.99 ± 3.52	23.24 ± 1.59	70.43 ± 306.35	
ID-TLR	11.9 % (13/109)	10.2 % (11/108)	9.9 % (11/111)	0.63
ΔPLGF (pg/mL)	−11.15 ± 11.03	0.58 ± 1.85	25.73 ± 113.29	
ID-TLR	9.6 % (10/104)	12.3 % (13/106)	11.2 % (12/107)	0.71
Vasodilators				
CGRP (pg/mL) at 30 days	162.02 ± 0.00	N/A	2860.35 ± 5039.08	
ID-TLR	11.9 % (30/252)	N/A	6.6 % (5/76)	0.19
ΔCGRP (pg/mL)	−194.07 ± 1336.27	N/A	1722.87 ± 2791.55	
ID-TLR	11.9 % (32/260)	N/A	7.1 % (4/56)	0.31
Markers of myocardial injury				
hFABP (ng/mL) at 30 days	0.23 ± 0.11	0.70 ± 0.16	8.03 ± 40.29	
ID-TLR	13.8 % (15/109)	9.2 % (10/109)	9.0 % (10/111)	0.26
ΔhFABP (ng/mL)	−11.79 ± 15.91	−1.05 ± 0.62	4.35 ± 23.38	
ID-TLR	15.2 % (16/105)	7.7 % (8/104)	10.1 % (11/109)	0.24
MPO (ng/mL) at 30 days	−191.10 ± 56.06	−79.94 ± 23.38	24.77 ± 72.17	
ID-TLR	10.2 % (11/108)	15.6 % (17/109)	6.3 % (7/111)	0.35
ΔMPO (ng/mL)	−92.11 ± 2.09	−78.00 ± 8.91	147.74 ± 580.14	
ID-TLR	14.3 % (15/105)	10.6 % (11/104)	8.3 % (9/108)	0.17

ID-TLR ischemia driven target lesion revascularization, other abbreviations as in Tables 3, 4, and 5

Table 7 Independent predictors of 3-year TLR and in-stent late loss at 13-months

Variable	Hazard ratio (95 % confidence interval)		*p* Value
3-Year TLR			
Lesion length (per mm)	1.03 (1.00–1.05)		0.02
CT-1 at admission (per 100 pg/mL)	0.76 (0.59–0.98)		0.04
	Coefficient	Standard error	
13-Month in-stent late loss			
Lesion length	0.017	0.00449	<0.01
Reference vessel diameter	0.163	0.08341	0.05
MMP9 (30 days) (100 units increment)	−0.0903	0.0461	0.05
MPO (30 days) (100 units increment)	−0.127	0.0578	0.03
MCP-1 (Delta) (100 units increment)	−0.214	0.0960	0.03

with clinical and/or angiographic restenosis after PES implantation for STEMI. Larger prospective trials to confirm and validate the utility of these biomarkers are warranted.

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