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Relationship between biomarkers and subsequent bleeding risk in ST-segment elevation myocardial infarction patients treated with paclitaxel-eluting stents: a HORIZONS-AMI substudy

Wouter J. Kikkert · Bimmer E. Claessen · Gregg W. Stone · Roxana Mehran · Bernhard Witzenbichler · Bruce R. Brodie · Jochen Wöhrle · Adam Witkowski · Giulio Guagliumi · Krzysztof Zmudka · José P. S. Henriques · Jan G. P. Tijssen · Elias A. Sanidas · Vasiliki Chantziara · Ke Xu · George D. Dangas

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Abstract Major bleeding complications in STEMI patients result in significant mortality, morbidity and healthcare cost. Identification of patients at increased risk of bleeding is therefore essential. New biomarkers might be of incremental value to identify patients at risk for bleeding after primary PCI. A total of 26 biomarkers were measured at enrolment and analyzed at a central core laboratory in 464 STEMI patients in the HORIZONS-AMI trial. We investigated the relationship between tertiles of biomarker and in hospital non-CABG major bleeding. In hospital non-CABG major bleeding occurred in 3.7 % of patients ($n = 17$). Increasing levels of cystatin C and D-dimer at admission were associated with higher rates of in hospital major bleeding. After adjustment for a risk score for bleeding, the odds ratio for in hospital major bleeding was 3.13 for cystatin C > 2.04 mg/L ($p = 0.046$) and 3.28 for ESAM > 34 ng/mL ($p = 0.037$). In this exploratory analysis of the HORIZONS-AMI biomarker substudy, high cystatin C and ESAM levels were associated with a higher risk of major bleeding. Larger studies are warranted to confirm the prognostic value of cystatin C and ESAM for major bleeding in STEMI patients.

Keywords Biomarkers · Drug eluting stents · Major bleeding · Primary percutaneous coronary intervention

Abbreviations

MI	Myocardial infarction
pPCI	Primary percutaneous coronary intervention

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W. J. Kikkert · B. E. Claessen · J. P. S. Henriques · J. G. P. Tijssen
Academic Medical Center—University of Amsterdam, Amsterdam, Netherlands

B. E. Claessen · G. W. Stone · R. Mehran · E. A. Sanidas · V. Chantziara · K. Xu · G. D. Dangas
Cardiovascular Research Foundation, New York, NY, USA

G. W. Stone · E. A. Sanidas · V. Chantziara
Columbia University Medical Center, New York, NY, USA

R. Mehran · G. D. Dangas
Mount Sinai Medical Center, New York, NY, USA

B. Witzenbichler
Charité Universitatsmedizin Campus Benjamin Franklin, Berlin, Germany

B. R. Brodie
LeBauer CV Research Foundation, Greensboro, NC, USA

J. Wöhrle
University of Ulm, Ulm, Germany

A. Witkowski
National Institute of Cardiology, Warsaw, Poland

G. Guagliumi
Ospedali Reuniti di Bergamo, Bergamo, Italy

K. Zmudka
Szpital Jana Pawla II, Krakow, Poland

G. D. Dangas (✉)
Mount Sinai Medical Center, Cardiovascular Institute, One Gustave L. Levy Place, P.O. Box 1030, New York, NY 10029, USA
e-mail: gdangas@crf.org; george.dangas@mssm.edu

STEMI	ST-segment elevation myocardial infarction
GPI	Glycoprotein IIb/IIIa inhibitor
CABG	Coronary artery bypass grafting
BMS	Bare metal stent
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

Introduction

Antithrombotic therapy reduces the rates of death, recurrent myocardial infarction (reMI) and stroke after primary percutaneous coronary intervention (pPCI) for patients with ST-segment elevation myocardial infarction (STEMI) [1–5]. Antithrombotic agents inhibit platelet aggregation or the coagulation cascade. These agents reduce thrombotic events but they also increase the risk of bleeding [2, 6]. Bleeding complications have consistently been shown to increase the risk of death, reMI and stroke both in large real world registries as well as in the setting of randomized trials [7–10]. Also, bleeding complications, both major and minor, have an adverse impact on the duration of hospitalization and combined with the additional resources required for the diagnosis and management of the hemorrhage result in a significant impact on healthcare cost. Therefore, the identification of patients at risk for bleeding has become a well focused clinical goal.

Patient, treatment and procedural characteristics associated with an increased risk of bleeding have been previously identified [11, 12], but whether new biomarkers are of incremental value to further define the patient at risk of bleeding has not been investigated. We therefore performed an exploratory study to investigate the relationship between 26 inflammatory and hematologic biomarkers and bleeding in STEMI patients treated with pPCI and drug-eluting stents (DES) in the formal prespecified biomarkers substudy of the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial.

Methods

The design and results of the HORIZONS-AMI trial have been previously published [4, 13–15]. Briefly, 3,602 STEMI patients were randomized open-label in a 1:1 ratio to treatment with bivalirudin alone (1,800 patients) or with unfractionated heparin (UFH) plus a glycoprotein IIb/IIIa inhibitor (GPI) (1,802 patients). Consecutive patients $\geq$18 years of age who presented within 12 h after the onset of symptoms and who had $\geq$1 mm ST-segment elevation in two or more contiguous leads, new left bundle-branch block, or true posterior myocardial infarction were eligible for enrolment. 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, those patients assigned to PCI patients were randomized again, in a 3:1 ratio, to either paclitaxel-eluting stents (PES, TAXUS Express, Boston Scientific, Natick, Ma) or an uncoated, but otherwise identical bare metal stent (BMS) (Express, Boston Scientific, Natick, MA). Aspirin (324 mg given orally or 500 mg administered intravenously) was given in the emergency room, after which 300–325 mg was given orally every day during the hospitalization, and 75–81 mg every day thereafter indefinitely. A 300–600 mg loading dose clopidogrel or 500 mg ticlopidine 500 mg (in the case of allergy to clopidogrel), was administered before catheterization, followed by 75 mg orally every day for at least 6 months. Follow-up angiography was performed routinely in a prespecified fraction of patients. Clinical follow-up was planned at 30 days, 6 and 12 months, and then yearly for 3 years total. The three year results of the HORIZONS AMI trial have been published previously [15].

Biomarkers substudy

A total of 502 patients within the angiographic follow-up cohort of the main trial who were randomized to receive PES were enrolled in the pre-specified biomarker substudy after appropriate additional written informed consent was obtained. Details of this cohort have been previously published [16]. Venous blood samples were obtained at study enrolment, hospital discharge, 30 days and 1 year. A total of 26 inflammatory and thrombotic biomarkers were measured. The present analysis was restricted to patients with available baseline biomarker measurements.

Biomarker assays

Biomarker values were determined by Alere Inc., San Diego, CA, using either Luminex or microtiter immunoassay methods. Detailed information regarding the immunoassays has been previously published and is presented in online resource 1 [16].

Study endpoints and definitions

The objective of the present analysis was to investigate the relationship between admission biomarker levels and the occurrence of in hospital non-CABG major bleeding. Major bleeding was defined as any bleeding that met the following criteria: intracranial bleeding, intraocular bleeding, retroperitoneal bleeding, access site hemorrhage requiring surgery or a radiologic or interventional procedure, hematoma $\geq$5 cm in diameter at the puncture site, reduction in hemoglobin concentration of $\geq$4 g/dL without an overt source of bleeding, reduction in hemoglobin concentration of $\geq$3 g/dL with an overt source of bleeding, reoperation for bleeding, or use of any blood product transfusion [13].

Anaemia was defined using WHO criteria as a hematocrit value at initial presentation <39 % for men and <36 % for women [17]. Thrombocytopenia was defined as less than 150,000 platelets per cubic millimeter at baseline (notably, a baseline platelet count under 100,000/cc3 was an exclusion criterion). Creatinine clearance was calculated at baseline by the Cockcroft-Gault equation [18].

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. For the purpose of the current analysis, patients were divided into tertiles according to biomarker values at admission. Of the 26 biomarkers determined, 5 had a detection threshold, below which the biomarker was unmeasurable. Patients with a value below the detection threshold for these biomarkers were categorized in the lowest tertile.

Rates of in hospital major bleeding were compared using the X^2 statistic. For biomarkers with a significant association by the X^2 test, unadjusted odds ratios (ORs) for in hospital major bleeding were calculated using logistic regression models. The two tertiles with the lowest event rates were considered the reference category. Biomarkers that were significantly associated with in hospital major bleeding by univariate analysis were included in multivariate logistic regression analyses adjusting for a risk score for bleeding by Mehran et al. [12]. This bleeding risk score proposed by our group is an integer score derived from the following 6 baseline characteristics that were predictive of non-CABG major bleeding in the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial and HORIZONS-AMI trial: age, gender, white blood cell count, serum creatinine (mg/dL), anemia, antithrombotic therapy (bivalirudin vs UFH + GPI) and presentation (STEMI vs NSTEMI) [12]. All the Biomarkers that remained statistically significant after adjustment for the Mehran risk score, were then entered in a final model together with the Mehran risk score. Entry and exit criteria were set at $p = 0.10$.

Results

The patient flow chart of the HORIZONS-AMI biomarkers substudy is depicted in Fig. 1. Of the 3,062 patients randomized in the HORIZONS AMI trial, 502 were enrolled in the formal biomarker substudy (501 patients received a paclitaxel eluting stent). Online Resource 2 presents baseline characteristics for patients included in the biomarker substudy, compared to those not in the biomarker substudy.

Baseline biomarker measurements were obtained in 464 patients of the 502 patients in the biomarker substudy. Of these 464 patients, 17 patients (3.7 %) suffered an in-hospital non-CABG major bleeding. Baseline characteristics of patients according to in-hospital bleeding status are given in Table 1. Patients who suffered a major bleeding were older, more often female, more frequently had diabetes and had a lower creatinine clearance at baseline. Moreover, those with a major bleeding more often had a history of congestive heart failure and more frequently had a decreased left ventricular ejection fraction (LVEF <40 %) at presentation. Finally, patients who suffered an in hospital major bleeding were more frequently treated with a 300 mg loading dose clopidogrel (rather than 600 mg), and were more often treated with a GP IIb/IIIa inhibitor.

Association between biomarkers at enrolment and in hospital non-CABG major bleeding

Cut-off values for the tertiles of biomarkers determined at enrolment are given in the Online Resource 3. The rates of in hospital non CABG major bleeding according to tertiles of admission biomarker are given in Table 2. Increasing levels of Interleukin-6 (IL-6), Interleukin-1β (Il-1 β), D-dimer, cystatin C and ESAM were associated with increasing rates of in hospital major bleeding. Table 3 presents the univariable and multivariable logistic regression analyses for the biomarkers with a significant relationship by the X^2 test. After adjustment for the previously proposed bleeding risk score, a serum ESAM level

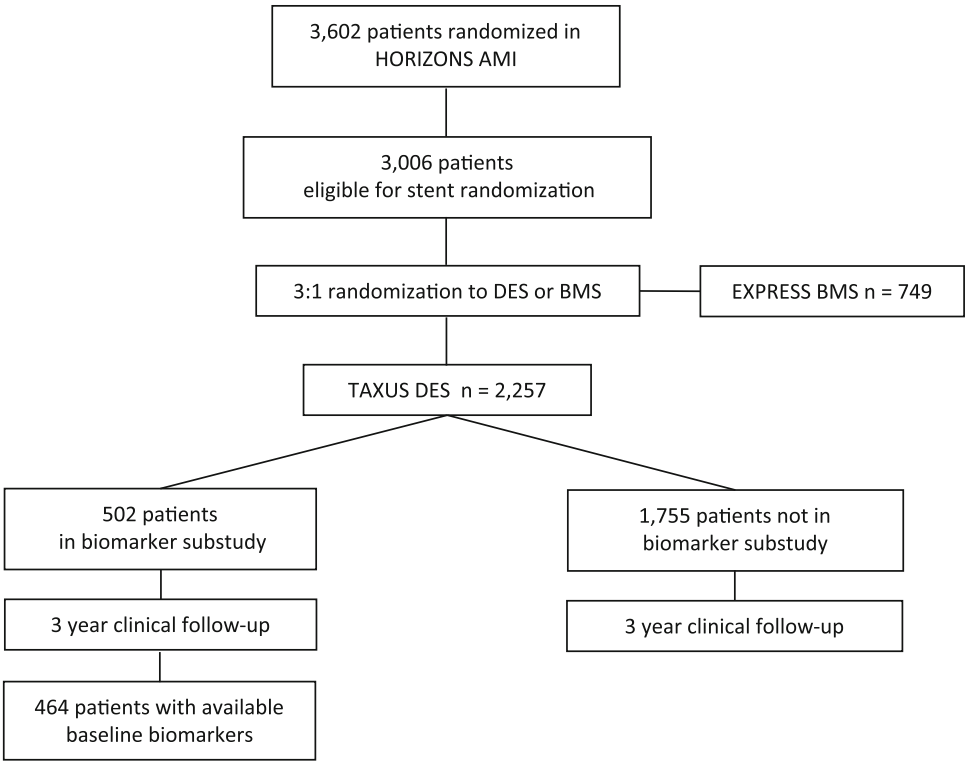

Fig. 1 Patient flow chart

Table 1 Demographic, procedural and treatment characteristics in patients with and without in hospital non CABG major bleeding in the biomarker substudy

	In hospital major bleeding		
	Yes ($n = 24$)	No ($n = 447$)	p Value
Age in years	73.2 [57.0–81.5]	59.7 [51.1–68.1]	0.012
Female	47.1 (8/17)	19.5 (87/447)	0.011
Diabetes	35.3 (6/17)	13.6 (61/447)	0.024
IDDM	11.8 (2/17)	3.1 (14/447)	0.11
Hypertension	52.9 (9/17)	53.0 (237/447)	0.99
Hyperlipidemia	29.4 (5/17)	42.5 (190/447)	0.28
Body mass index—median (IQR)	25.7 (24.4–29.1)	27.4 (24.7–30.4)	0.43
Current smoker	47.1 (8/17)	49.7 (222/447)	0.83
Anemia[a]	13.3 (2/15)	10.5 (46/437)	0.67
Creatinine clearance (mL/min/1.73 m^2)[b]	59.8 [46.5–84.4]	96.4 [74.5–120.7]	0.0012
Leucocyte count (giga/L)	12 [9–13]	11 [8–13]	0.30
Thrombocytopenia[c]	12.5 (2/16)	3.4 15/435)	0.14
Previous MI	11.8 (2/17)	5.8 (26/447)	0.27
Previous PCI	5.9 (1/17)	7.4 (33/447)	1.00
Previous CABG	0.0 (0/17)	1.6 (7/447)	1.00
Killip class >1	17.6 (3/17)	5.6 (23/447)	0.076
History of CHF	23.5 (4/17)	3.4 (15/447)	0.0034
Risk score bleeding—median (IQR)	22.0 (15.0–26.0)	12.0 (9.0–18.0)	0.0002
Procedural characteristics			
Symptom onset to balloon (median [IQR]), hours)	300 [156–348]	215 [153–320]	0.23
LVEF <40 %	43.8 (7/16)	11.1 (44/395)	0.0014
Infarct related artery[d]			

Table 1 continued

	In hospital major bleeding		
	Yes ($n = 24$)	No ($n = 447$)	p Value
LAD	57.9 (11/19	38.0 (185/487)	0.081
RCX	15.8 (3/19)	15.4 (75/487)	1.00
RCA	26.3 (5/19)	45.8 (223/487)	0.094
SVG	0	0.8 (4/487)	1.00
Closure device used	25.0 (5/16)	43.1 (186/432)	0.15
Antithrombotic treatment			
Peak ACT	338 [294–400]	315 [263–383]	0.30
Aspirin			
Before admission	11.8 (2/17)	21.5 (96/447)	0.54
During hospitalization	100 (17/17)	100 (447/447)	N/A
Loading dose clopidogrel			
300 mg	52.9 (9/17)	27.3 (122/447)	0.028
600 mg	47.1 (8/17)	71.8 (321/447)	0.052
Heparin before procedure	76.5 (13/17)	78.1 (349/447)	0.77
Antithrombin during procedure			
Heparin	64.7 (13/17)	49.2 (220/447)	0.21
Bivalirudin	35.3 (6/17)	51.2 (229/447)	0.20
Glycoprotein IIb/IIIa inhibitor use	82.4 (14/17)	53.5 (239/447)	0.019
In hospital warfarin use	11.8 (2/17)	2.0 (9/447)	0.057

IDDM indicates insulin dependent diabetes, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *CHF* congestive heart failure, *IQR* interquartile range, *LVEF* left ventricular ejection fraction, *LAD* left anterior descending artery,*RCX* ramus circumflexus, *RCA* right coronary artery, *SVG* saphenous vein graft, *ACT* activated clotting time

[a] Anemia was defined as baseline hematocrit less than 39 for males and less than 36 for females

[b] Creatinin clearance was calculated with the Cockcroft Gault equation

[c] Thrombocytopenia was defined as less than 150,000 cells per cubic millimeter at baseline

[d] The Mehran risk score is an integer score derived from the following 6 baseline characteristics that were predictive of non–CABG major bleeding in the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial and HORIZONS-AMI trial: age, gender, white blood cell count, serum creatinine (mg/dL), anemia, antithrombotic therapy (bivalirudin vs UFH + GPI) and presentation (STEMI vs NSTEMI) [12]. Multiple vessels for each patient are possible

$\geq$34.3 ng/mL was associated with a OR of 3.28 ($p = 0.037$) for in hospital non-CABG major bleeding. Similarly, a cystatin C level $\geq$2.04 mg/L was associated with a OR of 3.13 ($p = 0.046$) for in hospital non-CABG major bleeding. In a logistic regression model, including cystatin C, ESAM and the Mehran risk score, the OR for major bleeding was 2.58 for ESAM $\geq$ 34.3 ng/mL (95 % CI 0.81–8.25, $p = 0.11$), and 2.34 for cystatin C $\geq$2.04 mg/L (95 % CI 0.74–7.70, $p = 0.15$). The OR for the risk score for bleeding in this model was 1.11 (95 % CI 1.04–1.18, $p = 0.0023$) per unit increase.

Discussion

In this exploratory analysis of the formal prespecified biomarker substudy of the large scale HORIZONS-AMI trial, we sought to identify biomarkers that were associated with the risk of bleeding. At baseline, a cystatin C level >2.04 mg/L and an ESAM level >34.3 ng/mL resulted in a 2.5- to three-fold increase in risk for in hospital non-CABG major bleeding. Intriguingly, ESAM has been demonstrated to be involved in thrombosis and hemostasis in preclinical research. Cystatin C has previously been shown to predict cardiovascular mortality and adverse outcome after acute myocardial infarction. To our best knowledge our study is the first study describing an increased bleeding risk in patients with high cystatin C levels.

ESAM is a member of the immunoglobulin family known to contribute to hematopoiesis, angiogenesis, and leucocyte extravasation [19–21]. In addition, ESAM contributes to vascular permeability, which was shown to contribute to bleeding in a rabbit model [21, 22]. Moreover, ESAM expression is enhanced after platelet activation [23]. Interestingly, ESAM has also been found to downregulate thrombus growth in both zebrafish and mice

Table 2 In hospital non-CABG major bleeding by tertiles of biomarkers measured upon admission

Biomarker	First tertile % (*n*/*N*)	Second tertile % (*n*/*N*)	Third tertile % (*n*/*N*)	*p* Value
Cytokines				
IL-6	1.3 (2/152)	4.0 (6/151)	5.8 (9/156)	0.046
IL-8[a]	3.1 (10/323)	0.0 (0/0)	5.1 (7/136)	0.29
CCL23	2.0 (3/152)	4.6 (7/152)	4.5 (7/156)	0.25
CT-1	3.3 (5/151)	2.6 (4/153)	5.1 (8/156)	0.37
IL-18	1.3 (2/152)	4.6 (7/151)	5.1 (8/156)	0.085
IL-1β[a]	1.8 (4/218)	3.4 (3/87)	6.4 (10/156)	0.028
IL-1ra	2.0 (3/152)	3.3 (5/151)	5.8 (9/155)	0.083
MCP-1	5.3 (8/152)	0.7 (1/151)	5.1 (8/157)	0.96
IL-12[a]	4.1 (13/320)	0.0 (0/0)	2.8 (4/144)	0.50
Matrix metalloproteinases				
MMP9	5.3 (8/151)	3.3 (5/153)	2.6 (4/156)	0.21
PAPP-A	2.6 (4/153)	2.0 (3/152)	6.4 (10/156)	0.083
Growth factors				
PLGF	2.6 (4/151)	3.9 (6/153)	4.5 (7/156)	0.40
Vasodilators				
CGRP[a]	3.1 (12/381)	0.0 (0/0)	6.3 (5/80)	0.19
BNP	2.0 (3/152)	3.3 (5/152)	5.8 (9/156)	0.084
proANP[a]	2.8 (6/213)	2.2 (2/93)	5.8 (9/155)	0.16
Adinopponectin	2.6 (4/153)	3.9 (6/154)	4.5 (7/157)	0.39
Angiotensinogen	2.6 (4/153)	3.9 (6/154)	4.5 (7/157)	0.39
Acute phase proteins				
CRP	2.6 (4/154)	4.6 (7/153)	3.8 (6/157)	0.57
Renal function markers				
Cystatin-C	1.3 (2/154)	2.0 (3/152)	7.6 (12/158)	0.0062
Thrombotic biomarkers				
D-dimer	1.3 (2/154)	2.6 (4/151)	7.1 (11/156)	0.012
vWF	3.3 (5/153)	4.6 (7/153)	3.2 (5/158)	0.96
Adhesion molecules				
ESAM	2.0 (3/152)	1.3 (2/151)	7.6 (12/157)	0.012
ICAM	2.6 (4/154)	3.9 (6/153)	4.5 (7/157)	0.39
VCAM	5.8 (9/154)	2.0 (3/152)	3.2 (5/158)	0.22
Markers of myocardial injury				
hFABP	2.6 (4/153)	3.9 (6/152)	4.5 (7/156)	0.39
MPO	4.6 (7/152)	1.3 (2/151)	5.1 (8/156)	0.80

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

[a] Patients with a value below the detection threshold were stratified in the lowest tertile

[24, 25]. In a study by Stalker et al., thrombus aggregation and growth was enhanced in ESAM knockout mice, both in vivo and in vitro. After dissection of the distal part of the tail, there was no difference in bleeding time between ESAM knockout mice and their wild counterparts, but rebleeding occurred significantly less often in the ESAM knockout mice [25]. In our study, higher levels of ESAM were associated with higher rates of bleeding. This finding is consistent with the fact that ESAM has a downregulating effect on thrombus growth and hemostasis in both zebrafish and mice, suggesting that ESAM may be involved in human thrombosis and hemostasis.

Cystatin C is a low-molecular-weight cysteine protease inhibitor that is produced at a constant rate in all nucleated cells and, because of its small size, freely filtered by the glomerulus [26]. It is not secreted, but it is reabsorbed in the proximal tubule, where it is catabolised by epithelial cells, so that it does not return to the blood stream [27]. Therefore cystatin C is a near perfect marker of the glomerular filtration rate (GFR). Some studies have reported cystatin C to be an equivalent or an even more accurate marker of GFR than estimations based on creatinin such as the Cockcroft Gault (CG) or Modification of Diet in Renal Disease (MDRD) calculations [28]. Cystatin C was shown

Table 3 Univariate and multivariate associations between admission biomarker levels and in hospital major bleeding

Logistic regression models for in hospital non CABG major bleeding									
	Unadjusted[a]			Adjusted[b]			Adjusted[c]		
Biomarker	OR	95 % CI	*p* value	OR	95 % CI	*p* value	OR	95 % CI	*p* value
IL-6	2.38	0.90–6.29	0.081	1.63	0.58–4.58	0.36	–	–	–
IL-1β	3.04	1.13–8.15	0.027	2.27	0.81–6.38	0.12	–	–	–
Cystatin C	5.15	1.78–14.9	0.0025	3.13	1.02–9.64	0.046	2.34	0.74–7.70	0.15
D-dimer	3.82	1.39–10.5	0.0096	1.81	0.58–5.61	0.30	–	–	–
ESAM	5.14	1.78–14.9	0.0025	3.28	1.07–10.01	0.037	2.58	0.81–8.25	0.11

OR denotes odds ratio, *CI* confidence interval, other abbreviations as in Table 2

[a] Unadjusted odds ratios were calculated using univariate logistic regression models

[b] Adjusted odds ratios were calculated using logistic regression analyses, adjusting for the Mehran risk score for bleeding [12]

[c] Adjusted odds ratios were calculated using logistic regression analysis, including the Mehran risk score and the biomarkers that were significant after adjustment for the Mehran risk score

to be an independent predictor of death or myocardial infarction in patients with stable coronary artery disease, acute coronary syndromes and STEMI [29–33]. In the present analysis a cystatin C level >2.04 mg/L was associated with a 2.5- to three-fold increase in risk for in-hospital bleeding. This novel finding is in line with previously published work showing an increased risk of bleeding and adverse outcome in patients with decreased renal function (defined as creatinine clearance <60 mL/min) [34]. The excess risk of bleeding in patients with renal dysfunction is attributable to reduced clearance of antithrombotic agents and a hypocoagulable and hypoaggregable state secondary to abnormalities in the coagulation cascade, inhibited platelet activity, decreased functional platelet expression of GP IIb/IIIa receptors and inhibited platelet-endothelial interaction [35–39].

Limitations

A number of limitations of this study must be addressed. We analyzed the relationship between serum biomarker levels and the occurrence of major bleeding 26 times. The possibility of spurious significant results due to chance can therefore not be excluded as we applied no formal statistical correction for multiple comparisons. Second, in hospital non-CABG major bleeding occurred in only 17 patients with available admission biomarkers. Therefore, we had limited ability to adjust for confounding variables. However, we adjusted for an integer risk score derived of 6 variables with a strong predictive value for bleeding. Thus, imbalances in baseline characteristics predictive of bleeding were largely accounted for. However, although the Mehran risk score is calculated by assigning integer points for 6 variables strongly associated with the risk of bleeding, it is possible that after adjustment for this risk score, differences in the individual components of the risk score with high and low biomarker levels remain. Although there did appear to be a relationship between several biomarkers and bleeding, these relationships did not reach statistical significance, possibly due to limited amount of patients included in this biomarker substudy. We could not address the relationship between discharge, 30 day and 1 year biomarker levels and subsequent bleeding, as there were only seven non-CABG major bleedings occurring between discharge and 3 years follow-up.

Finally, as 99.9 % of patients (501/502) in the biomarker substudy of the HORIZONS-AMI were treated with PES, our results cannot directly be extrapolated to AMI patients treated with BMS or other DES such as everolimus-eluting stents. Also, all patients underwent primary PCI for STEMI, and our results may therefore not be applicable to ACS patients.

Conclusion

In this exploratory analysis of the formal HORIZONS-AMI biomarker substudy, two new biomarkers were associated with the occurrence of in hospital non-CABG major bleeding. Cystatin C >2.04 mg/L and ESAM >34.3 ng/mL resulted in a 2.5- to three-fold increase in risk for major bleeding. A larger trial is warranted to confirm the prognostic value of cystatin C and ESAM for bleeding after acute MI.

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