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Independent Predictors of Major Adverse Events following Coronary Stenting over 28 Months of Follow-Up

Elena Z. Golukhova[a] Marina V. Grigorian[a] Mariya N. Ryabinina[a]
Naida I. Bulaeva[a] Seth Fortmann[a] Victor L. Serebruany[b]

[a]Bakoulev Cardiovascular Research Center, Moscow, Russia; [b]Research Laboratories, Johns Hopkins University, Towson, Md., USA

Key Words
Coronary artery stenting · Platelet aggregation · Stent thrombosis · Stent restenosis · Plasminogen activator inhibitor -1 · von Willebrand factor · Dual antiplatelet therapy

Abstract
Background: Despite recent advances in stent design and constantly improving protective pharmacological strategies, complications and adverse events following percutaneous coronary interventions (PCI) are still major factors influencing morbidity and mortality. Therefore, predicting secondary vascular occlusions represents an unmet medical need. ***Objective:*** The aim of our study was to triage clinical and laboratory predictors of major adverse clinical events (MACE) following coronary stenting. ***Methods:*** This was a prospective, case-controlled, single-center study, which included 94 consecutive patients with documented coronary disease who underwent PCI with drug-eluting stent (DES) implantation. All patients received dual antiplatelet therapy with aspirin and clopidogrel. Numerous clinical characteristics and laboratory biomarkers were assessed before stenting and were correlated with poststenting MACE over the mean follow-up of 28 months. MACE included death, nonfatal myocardial infarction, target vessel revascularisation, stroke, stent thrombosis, angina recurrence and instent restenosis. ***Results:*** Twenty-three patients experienced MACE. Independent MACE predictors after PCI with DES implantation were antecedent diabetes mellitus (RR = 0.45; 95% CI 0.20–0.97; p = 0.045), prior thrombolytic therapy (RR = 0.42; 95% CI 0.27–0.83; p = 0.039), baseline plasminogen activator inhibitor -1 (PAI-1; p = 0.008) and plasma von Willebrand factor (vWF) activity (p = 0.007). Other clinical characteristics and laboratory indices showed no correlation with MACE. ***Conclusions:*** Background diabetes mellitus, prior thrombolytic therapy, PAI-1 and vWF prestenting activity may be useful for MACE prediction over 28 months of follow-up.

Introduction

In patients with acute coronary syndromes (ACS), vascular stenting remains the preferred treatment, with modern cardiologists applying novel techniques (i.e. hybrids, robotics, minimally invasive, drug-eluting and bio-

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Dr. Serebruany
HeartDrug™ Research Laboratories, Johns Hopkins University, Osler Medical Building
7600 Osler Drive, Suite 307
Towson, MD 21204 (USA)
E-Mail heartdrug@aol.com

resorbable devices) requiring complex pharmacological protection. Despite such advances, studies in Europe [1] and the USA [2] still report high incidences of complications and/or adverse events following coronary stenting. Predicting survival and triaging high-risk cohorts for secondary thrombotic occlusions and/or bleeding represent critical unmet medical needs. Therefore, a strong and broad effort is ongoing to identify reliable biomarkers indicative of future major adverse clinical events (MACE). Unfortunately, in real-life clinical scenarios, the practical utilization of predictive models is quite limited and many reports are pessimistic, suggesting marked discrepancies between interventional cardiologists' estimates and the established theoretical prediction models, scores or biomarkers [3–5]. Furthermore, the data are very scarce with regard to the potential association of antiplatelet therapy and future MACE predictions. Optimal platelet inhibition with dual antiplatelet therapy (DAPT) is a contemporary issue for patients undergoing percutaneous coronary intervention (PCI), and high on-treatment platelet reactivity may impact future adverse cardiac events after stent implantation [6, 7]. Clopidogrel response varies widely among patients and can be mediated by various clinical, genetic and cellular factors. Such clinical factors include ACS, diabetes mellitus, age, obesity, inflammation and renal and heart failure [7]. Understandably, the link between PCI outcomes, platelet activity and bleeding is better explored logistically, as it may be suggestive of some clinically adverse association(s) [8–10]. However, how such an adverse association will translate to clinical practice is unclear. In this prospective, single-center observational study, we tested whether background pre-PCI clinical and/or laboratory indices are predictive of MACE after drug-eluting stent (DES) implantation.

Methods

The study design was approved by the local Ethics Committee, and all patients provided a written informed consent. The index prospective single-center study included 94 patients with stable coronary artery disease admitted to Bakoulev Cardiovascular Center (Moscow, Russia) from 2009 to 2012. All patients underwent elective PCI based on the documented evidence of ischemia by treadmill-test. DAPT consisted of aspirin, a 325-mg loading-dose followed by 100 mg/day, and clopidogrel, a 600-mg loading-dose followed by 75 mg/day. Blood samples were collected, and PCI was performed within 24 h before receiving the loading doses of the antiplatelet agents. Exclusion criteria were as follows: ACS, aspirin and/or clopidogrel intolerance, recent trauma or extensive surgery within 1 month prior to study commencement, a platelet count outside the range of 100–450 × 10^9/l, hematocrit <30%, hemoglobin <100 g/l, chronic renal failure (serum creatinine ≥2.0 mg/dl) or the presence of concomitant inflammation, active infection, systemic connective tissue disease or cancer. For our study, the composite end point consisted of cardiac death, nonfatal myocardial infarction, target vessel revascularisation, stroke, stent thrombosis (ST), angina recurrence and instent restenosis. All deaths were defined as cardiac if no other cause had been found. For ST, the Academic Research Consortium definitions (definite, probable, possible, acute, late and very late) were used. Clinical follow-up after PCI was performed by telephone contact, a home visit or both.

Platelet aggregation was determined with a 2-channel laser analyzer 230LA NPF (Biola, Moscow, Russia). Platelet function was measured after the addition of 5 μmol/l adenosine diphosphate (ADP). Optimal DAPT response was defined as platelet aggregation by 5 μmol/l ADP <50%. VerifyNow® Assay (Accumetrics, San Diego, Calif., USA) is a point-of-care test that measures the rate and extent of changes in light transmittance caused by platelet aggregation in whole-blood samples. Arachidonic acid agonist was used to evaluate the antiplatelet action of aspirin, and the intensity of the transmitted light was converted in aspirin reaction units (ARU). The combination of ADP and prostaglandin E1 was used to assess receptor P2Y12 (clopidogrel) functionality, and data were expressed in P2Y12 reaction units (PRU). Reference values for optimal DAPT as recommended by the manufacturer were applied: ARU <550; PRU <208; P2Y12 receptor inhibition % >23.

High-sensitivity C-reactive protein levels in serum were determined using IMMAGE® System assay (Beckman Coulter, Galway, Ireland). Soluble (s)P-selectin levels were assessed using an ELISA assay for quantifying human sP-selectin in plasma (eBioscience, Vienna, Austria). Soluble CD40 ligand levels in plasma were quantitatively determined using an ELISA assay (eBioscience, San Diego, Calif., USA). High sensitivity IL-6 levels were assessed using an ELISA assay for the quantitative determination of human IL-6 in plasma (eBioscience, San Diego). For assessment of endothelial function, plasminogen activator inhibitor-1 (PAI-1) antigen levels in the plasma were evaluated using an ELISA assay from TECHNOZYM® PAI-1-antigen-ELISA (Technoclone GmbH, Vienna, Austria) and von Willebrand factor (vWF) antigen using an ELISA assay HemosIL von Willebrand Factor Antigen (IL Coagulation Systems, Bedford, Mass., USA). CYP2C19 genotyping was performed following the inclusion of the last participant to remove the possibility of affecting the DAPT regime. Genotyping was performed using kits SNP-Express RV Clopidogrel 1 and Clopidogrel 2 (Lytech, Moscow, Russia) with iCycler IQ5 (Bio-Rad, Hercules, Calif., USA) according to the manufacturers' protocols. Data are expressed as mean ± SD, and those with skewed distributions as the median value with a maximum-minimum range. Categorical data were presented as frequencies and percentages. Differences between 2 groups were tested with the Fisher exact test for categorical variables. Differences in continuous variables were analyzed by the unpaired Student t test or the Mann-Whitney U test. The Shapiro-Wilk test was used to assess the normal distribution of continuous data. A p value <0.05 was considered significant. All analyses were carried out with SPSS v17.0 (SPSS, Chicago, Ill., USA) and Statistica 8.0 (StatSoft Inc., Tulsa, Okla., USA).

Table 1. Demographics, clinical characteristics and laboratory indices

Characteristics	All patients (n = 94, 100%)	MACE-free (n = 71, 75.5%)	MACE (n = 23, 24.5%)	p value
Age, years	59 (35–76)	57 (35–76)	63 (43–75)	0.18
Males	81 (86.2)	60 (84.5)	20 (87.0)	0.77
BMI	28.7 (20.0–41.1)	28.1 (20.0–41.0)	29.0 (23.0–41.1)	0.22
Current smoker	56 (59.6)	46 (64.8)	10 (43.5)	0.07
Diabetes mellitus	19 (20.2)	11 (15.5)	8 (34.8)	**0.045**
Hypertension	86 (91.5)	63 (88.7)	23 (100)	0.09
Hyperlipidemia	59 (62.8)	46 (64.8)	13 (56.5)	0.48
Prior MI	51 (54.3)	38 (53.5)	13 (56.5)	0.80
Prior thrombolysis	26 (27.7)	3 (4.2)	4 (17.4)	**0.039**
Prior PCI	30 (31.9)	19 (26.8)	11 (47.8)	0.08
Stents >1	39 (42)	24 (34)	15 (65)	0.08
Medical therapy				
Aspirin	93 (98.9)	70 (98.6)	23 (100)	0.58
Clopidogrel	62 (66.0)	44 (62.0)	18 (78.3)	0.15
Statins	42 (44.7)	33 (46.5)	9 (39.1)	0.54
PPI	16 (17.0)	14 (19.7)	2 (8.7)	0.22
Ca-channel blockers	18 (19.1)	57 (80.3)	19 (82.6)	0.80
Echocardiography				
EF LV	62 (32–76)	62 (32–76)	63 (50–69)	0.25
Hypokinesis	26 (27.7)	23 (32.4)	4 (17.4)	0.17
Laboratory measurements				
Hemoglobin, g/l	142 (116–176)	142 (116–172)	145 (116–176)	0.72
Platelet count, 10^9/l	235 (126–400)	231 (134–390)	263 (126–400)	0.45
Hematocrit, %	43 (30–51.7)	42.9 (35.1–50.0)	44 (30.5–51.7)	0.46
Creatinine, μmol/l	90 (59–141)	90.0 (59.0–141.0)	90.0 (59.0–127.0)	0.64
Total cholesterol, mmol/l	4.89 (2.06–9.56)	4.88 (2.06–9.56)	5.0 (2.19–8.3)	0.87
LDL, mmol/l	2.9 (0.9–7.3)	2.9 (0.9–7.3)	2.8 (1.1–5.0)	0.71
Triglycerides, mmol/l	0.9 (0.5–1.7)	1.2 (0.4–3.0)	1.4 (0.4–15.0)	0.42
Glucose, mmol/l	1.28 (0.37–15)	5.32 (3.8–11.8)	5.64 (3.9–14.5)	0.40
On-treatment platelet reactivity				
LTA-5ADP, %	38.4 (7.0–65.0)	41.0 (7.0–63.0)	42.0 (13.0–65.0)	0.31
ARU	390 (250–591)	390 (250–391)	400 (290–585)	0.27
PRU	159 (25–336)	145 (25–336)	203 (59–321)	0.09
Base PRU	259.5 (88–386)	259.5 (88–344)	259 (59–321)	0.53
% of inhibition P2Y12	41 (0–98)	43 (0–98)	35 (1–72)	0.14
Proinflammatory and endothelial markers				
hs-CRP, mg/l	1.5 (0.2–17.7)	1.04 (0.16–17.7)	2.59 (0.39–17.4)	0.21
sP-selectin, ng/ml	56.1 (21–120)	56.6 (20–120)	50.9 (35.4–97.5)	0.39
sCD40 ligand, ng/ml	0.7 (0.06–10.7)	0.7 (0.06–10.7)	0.7 (0.06–5.39)	0.41
hs-IL-6, pg/ml	1.4 (0.16–9.76)	1.1 (0.16–9.76)	1.7 (0.37–8.22)	0.10
PAI-1, ng/ml	51 (4–124)	40.6 (3.9–113.9)	79.1 (8.8–124.0)	**0.008**
vWF activity, %	89 (47–189)	80 (46.7–180.0)	162 (54.1–89.1)	**0.007**
CYP2C19 genotype				
CYP2C19*2 carriage	27 (28.7)	20 (28.2)	7 (30.0)	0.83

Categorical data are presented as n (%). Continuous data are presented as median (min–max). Figures in bold type indicate significance. BMI = Body mass index; EF LV = ejection fraction of left ventricule; hs-CRP = high-sensitivity C-reactive protein; hs-IL-6 = high-sensitivity IL-6; LDL = low-density lipoprotein; LTA-5ADP = platelet aggregation with 5 μmol/l ADP; MI = myocardial infarction; PPI = proton pump inhibitors.

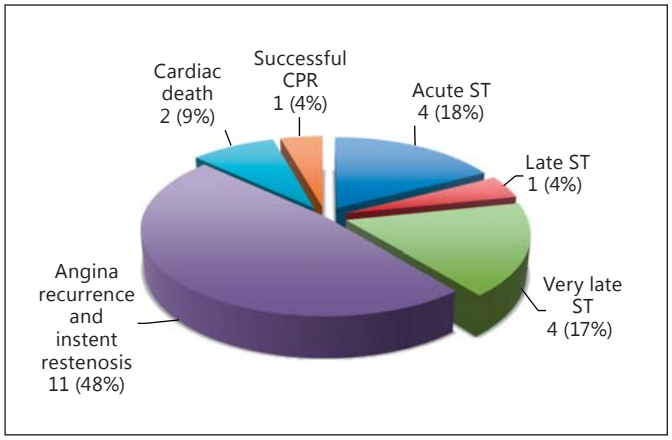

Fig. 1. Adverse cardiovascular events during the 28-month follow-up period. CPR = Cardiopulmonary resuscitation.

Results

Ninety-four patients were included in this study. Baseline clinical characteristics and comparison between patients with and without MACE are presented in table 1.

According to coronary angiography, 39 patients (41.5%) had three-vessel disease, 26 (27.7%) had two-vessel disease, 16 (17.0%) had single-vessel disease and 13 (13.8%) had multivessel lesions. All patients enrolled in this study underwent PCI with DES implantation. First-generation DES (sirolimus- and paclitaxel-eluting stents) were used in 46% of cases at the commencement of our study. Starting in 2011, second-generation DES (zotarolimus- and everolimus-eluting stents) were implanted in the remaining 54% of patients. The mean follow-up period was 28.2 ± 15.5 months. During our study, we did not register any instances of major bleeding. The composite MACE occurred during follow-up in 23 patients (24.5%). There were 2 deaths due to chronic heart failure deterioration. All 9 ST events occurred in the overall population during follow-up, 4 of which were acute (<24 h after PCI). The incidence and distribution of MACE are shown in figure 1.

Discussion

The main findings of our small observational study are the establishment of several clinical (diabetes and prior thrombolysis) and laboratory (PAI-1 and vWf) indices linking coronary interventions with delayed adverse vascular outcomes. With regard to biomarkers, the primary focus of the current research trend is a desperate attempt to find the association between heightened platelet activity and MACE following stent implantation. Discrepancies between the findings of observational studies exist, suggesting persistent residual platelet activity despite DAPT and multiple failed randomized trials to prove that tailored or guided therapies improve outcomes. There is compelling evidence that up to 50% of patients exhibit high residual platelet reactivity while on clopidogrel and aspirin [11, 12]. Previous reports have demonstrated an association between increased residual platelet reactivity and adverse events after PCI [13, 14]. In contrast, the results of 4, randomized, large-scale trials, GRAVITAS [15], TRIGGER-PCI [16], ADAPT-DES [17] and ARCTIC [18], failed to show significant improvement in patients undergoing PCI with a personalized approach to antiplatelet therapy.

This index study identified the background risk factors linked to MACE. According to the univariate regression analysis, concomitant diabetes mellitus, repeated therapy with thrombolytic agents, endothelial dysfunction assessed by heightened baseline PAI-1 levels and activity of vWF were independent predictors of adverse outcomes after PCI. Multiple reports have associated inflammatory biomarkers such as C-reactive protein [19], IL-6 [20, 21], vWf and several adhesion molecules [22] with the development of adverse cardiac events including ST and restenosis after PCI. However, our data failed to confirm the prognostic value of C-reactive protein in patients after PCI. This may be due to the fact that the majority of the studies reporting the said association were conducted in patients with ACS, while the patients in this study were stable. Additionally, we did not find evidence linking IL-6, sCD40L and sP-selectin with MACE after PCI. Current data on the prognostic impact of these markers in patients with stable coronary artery disease are rather scanty and contradictory as well as being heavily dependent on enrolment criteria, timing of blood draws and assay validation. ACS was an exclusion criterion of our study, and 66% of patients received clopidogrel and 45% were treated with statins before enrolment. These facts may partly explain the discrepancies between our index data and previously reported evidence. A recent, elegant meta-analysis study suggested that polymorphisms in the gene encoding PAI-1 increased the risk of myocardial infarction, resulting in increased PAI-1 activity [23]. Importantly, PAI-1 levels were associated with a higher risk of restenosis and ST after DES implantation [24]. Heper et al. [25] found that in patients with multivessel lesions re-

quiring multiple stents, there was an increase in the vWF expression in the coronary arteries; this may be of particular importance in the pathogenesis of subacute ST and restenosis. In the study conducted by Miura et al. [26] where 225 patients with chronic coronary artery disease were examined, vWf had a prognostic impact on adverse cardiovascular events; this supports our data fully. Additionally, our study found no significant impact of CYP2C19*2 carriage on the development of adverse cardiovascular events after PCI. Our findings differ from the large number of clinical studies suggesting a significant independent influence of CYP2C19*2 allele carriage on the risk of adverse outcomes after PCI. We propose that this inconsistency is due to the small study population and thus a small number of homozygous CYP2C19*2 carriers as well as the absence of patients with ACS.

Two limitations of this study should be mentioned. First, the sample size was rather small, and the study was carried out with an enrolment period of >2 years. Second, the MACE rate was high, which reflects the reality in underdeveloped countries. Nonetheless, the strengths of our study were uniformed enrolment rules, a single-center setup and a considerable follow-up duration of 28 months. We conclude that MACE after PCI were significantly associated with antecedent diabetes mellitus, prior thrombolysis, PAI-1 plasma levels ≥75.95 ng/ml and vWf activity ≥155.15%. Independent predictors of adverse cardiac events were diabetes mellitus, PRU ≥202, PAI-1 levels ≥75.95 ng/ml, and vWF activity ≥155.15%. In conclusion, optimization of clinical outcomes after PCI requires achieving a balance between the risks of thrombotic occlusions and bleeding complications in DAPT.

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