Correlation Between Point-of-Care Platelet Function Testing and Bleeding After Coronary Angiography According to Two Different Definitions for Bleeding

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Platelet function testing could be useful when assessing the risk for bleeding during treatment with antiplatelet drugs. This has been indicated in several studies, including the Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty—Bleeding (ARMYDA-BLEEDS) study, which demonstrated that testing with a point-of-care assay correlated with bleeding events after percutaneous coronary intervention. To standardize bleeding definitions, the Bleeding Academic Research Consortium (BARC) published a consensus report, which is in need of data-driven validation. Hence, the investigators conducted an observational, prospective, single-center study of 474 patients receiving clopidogrel and aspirin who underwent coronary angiography with or without percutaneous coronary intervention from October 2006 to May 2011. Platelet reactivity was measured with adenosine diphosphate—induced single-platelet function testing (Plateletworks) at the start of coronary angiography. The primary end point was the 30-day incidence of bleeding as defined by BARC and ARMYDA-BLEEDS. The aim of the present study was to investigate the relation between on-treatment platelet reactivity and the 30-day incidence of bleeding complications according to the BARC and ARMYDA-BLEEDS definitions. Patients in the first platelet aggregation quartile had a higher frequency of type 2 or higher BARC bleeding and ARMYDA-BLEEDS-defined bleeding <30 days after coronary angiography compared with the fourth quartile (16.9% vs 6.7%, $p = 0.014$, and 8.5% vs 1.7%, $p = 0.016$, respectively) and the third quartile (16.9% vs 7.7%, $p = 0.031$, and 8.5% vs 2.6%, $p = 0.048$, respectively). In conclusion, patients with low on-treatment platelet reactivity at the time of intervention had a significantly higher incidence of bleeding according to the BARC and ARMYDA-BLEEDS definitions <30 days after coronary angiography with or without percutaneous coronary intervention. **(Am J Cardiol 2014;114:1347—1353)**

The aim of this study was to investigate the relation between on-treatment platelet reactivity assessed with a point-of-care single-platelet function test and the 30-day incidence of bleeding complications, as defined by the Bleeding Academic Research Consortium (BARC)[1] and Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty—Bleeding (ARMYDA-BLEEDS)[2] definitions, after coronary angiography with and without percutaneous coronary intervention (PCI).

Methods

This observational prospective study initially included 491 patients who underwent coronary angiography with and without PCI at the Karolinska University Hospital from October 2006 to May 2011. The indications for coronary angiography were acute coronary syndromes, stable angina, or chest pain with high suspicion of coronary origin. Sixteen patients were excluded because of treatment with glycoprotein IIb/IIIa inhibitors before platelet function testing, and 1 patient was excluded because of treatment with prasugrel, leaving a study cohort of 474 patients. All patients not previously receiving clopidogrel and/or aspirin treatment received a loading dose of clopidogrel (150 to 800 mg) in addition to aspirin (300- to 500-mg loading dose, followed by 75 mg/day) before coronary angiography. If PCI was performed, a daily maintenance dose of clopidogrel 75 mg was postprocedurally recommended in addition to aspirin for 1 year in patients receiving drug-eluting stents, whereas 3 months of dual-antiplatelet treatment was recommended to patients receiving bare-metal stents. Patients already receiving clopidogrel treatment for >5 days before coronary angiography did not receive additional loading dose but continued with their daily maintenance dose (75 mg once daily).

Ten patients were receiving warfarin treatment, which was discontinued ≥7 days before coronary angiography. All interventions were performed according to international guidelines.[3,4] The femoral approach was used in all but 32 interventions, in which the radial approach was used, and unfractionated heparin was given in weight-adjusted doses

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Table 1
Demographic characteristics

Characteristic	1st Quartile (n = 118)	2nd Quartile (n = 119)	3rd Quartile (n = 117)	4th Quartile (n = 120)	p-Value*
Median [range] platelet aggregation	29% [0−46%]	63% [47−75%]	84% [75−91%]	96% [91−100%]	
Age (years)	63.9 ± 8.9	65.0 ± 11.2	65.9 ± 11.8	65.5 ± 10.9	0.20
Women	28 (24%)	31 (26%)	23 (20%)	23 (19%)	0.39
BMI (kg/m^2)	26.3 ± 5.0	26.9 ± 3.9	27.3 ± 5.4	28.7 ± 4.4	<0.001
Hypertension†	65 (55%)	62 (52%)	58 (50%)	73 (61%)	0.37
Diabetes mellitus	23 (19%)	35 (29%)	29 (25%)	32 (27%)	0.19
Current smokers	19 (16%)	24 (20%)	27 (23%)	21 (18%)	0.77
Prior myocardial infarction	33 (28%)	36 (30%)	36 (31%)	36 (30%)	0.73
Prior percutaneous coronary intervention	25 (21%)	20 (17%)	29 (25%)	26 (22%)	0.93
Prior coronary bypass	20 (17%)	18 (15%)	16 (14%)	15 (13%)	0.44
NCDR® CathPCI Bleeding Risk[5]					
Total score (points)	63.3 ± 20.4	65.8 ± 20.1	64.3 ± 21.3	65.0 ± 21.7	0.63
Low risk (<25)	—	1 (1%)	5 (4%)	3 (3%)	0.25
Medium risk (26−65)	66 (56%)	64 (54%)	63 (54%)	64 (53%)	0.69
High risk (>65)	52 (44%)	54 (45%)	49 (42%)	53 (44%)	0.99
Medication					
Clopidogrel LD (mg)					
150	—	1 (1%)	1 (1%)	1 (1%)	0.32
300	51 (43%)	59 (50%)	60 (51%)	64 (53%)	0.12
450	—	1 (1%)	2 (2%)	2 (17%)	0.50
600	22 (19%)	22 (18%)	22 (19%)	28 (23%)	0.38
800	—	1 (1%)	—	—	N/A
Time (hours) from LD to coronary angiography	47 [24/97]	69 [35/122]	45 [22/100]	27 [16/52]	<0.001
Time (hours) from last dose to coronary angiography	4.5 [2.5/6.0]	5.0 [3.0/6.0]	5.5 [3.5/6.5]	5.0 [3.0/7.0]	0.107
Clopidogrel maintenance treatment (months)	3 [1/3]	3 [0/3]	3 [0/3]	3 [1/3]	
Lipid-lowering drugs	102 (86%)	102 (86%)	96 (82%)	102 (85%)	0.75
Proton pump inhibitors	16 (14%)	23 (19%)	21 (18%)	16 (13%)	0.96
Fondaparinux	43 (36%)	47 (39%)	49 (42%)	52 (43%)	0.28
Bivalirudin	—	—	2 (2%)	1 (1%)	1.00

Data are expressed by number (percentage) for categorical variables, and as mean ± SD or median [25th/75th percentile] for continuous variables. Quartiles were established for the percentage of platelet aggregation measured by adenosine diphosphate-induced single-platelet aggregation.

LD = loading dose.

* Comparison between quartile 1 and quartile 4.

† Defined as documented and treated hypertension.

(50 to 100 IE/kg). The sheath size was 6Fr. A vascular closure device (Angio-Seal; St. Jude Medical, St. Paul, Minnesota) was used in 247 patients. A compression assist device (Femostop; St. Jude Medical) was used in the rest of the cohort and in patients with vascular closure devices when required for hemostasis. Use of periprocedural antiplatelet agents other than clopidogrel and aspirin, for example, glycoprotein IIb/IIIa inhibitors, was at the discretion of the interventionist.

At the start of each coronary angiographic procedure, a 4-ml blood sample was drawn from the arterial line. Assessment of adenosine diphosphate−induced platelet aggregation was performed by using single-platelet counting with the Plateletworks assay (Helena Laboratories, Beaumont, Texas). The test was always performed <10 minutes after blood sampling. The baseline platelet count was obtained by the addition of 1 ml whole blood to the first Plateletworks tube, primed with the synthetic anticoagulant ethylenediaminetetraacetic acid. One milliliter of whole blood was then added to the second Plateletworks tube, containing citrate and adenosine diphosphate (20 mmol), inducing platelet aggregation. For each tube, the platelet count was then measured with a cell counter (ABX Micros 60; Horiba ABX Diagnostics, Holliston, Massachusetts). Because platelet aggregates exceed normal platelet size, it is possible for the cell counter to discriminate between aggregated and nonaggregated platelets on the basis of size. The difference in platelet count between the 2 samples was used as a measurement of platelet aggregation. A research nurse, who was well familiar with the testing equipment and had received training from the manufacturer, conducted all blood sampling and subsequent platelet function testing. The physicians responsible for the patients during their hospital stays were not aware of the platelet function test results. Written informed consent was obtained from all patients. The regional human research ethics committee in Stockholm, Sweden, approved the study.

Data on in-hospital bleeding events were prospectively acquired, including location and extent, laboratory data, imaging data, medications, and treatment. The data on out-of-hospital bleeding events that did not require direct visits to health care professionals were registered at later routine follow-up visits. The study database and patients' medical records were reexamined for every bleeding event by 2 researchers blinded to platelet aggregation to classify them according to the bleeding definitions. The primary outcome was the 30-day incidence of bleeding complications after coronary angiography in relation to quartile distribution of