Mean Platelet Volume as a Predictor for Restenosis After Carotid Angioplasty and Stenting

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Background and Purpose—Platelet aggregation plays a vital role in the development of in-stent restenosis (ISR) after carotid angioplasty and stenting (CAS). Mean platelet volume (MPV) has been suggested as an index of platelet reactivity. This study aimed to investigate the association between MPV and ISR in CAS patients.

Methods—A total of 261 patients with CAS were enrolled. MPV was measured before CAS procedure. Digital subtraction angiography, computed tomographic angiography, or duplex ultrasonography was performed at 6 months and annually after the procedure. ISR was defined as ≥50% stenosis in the treated lesion. Cox regression was used to identify predictors of ISR after CAS.

Results—Of the 261 patients with CAS, 46 (17.6%) were determined with ISR during a mean follow-up of 12.1±16.1 months (range, 2.1–120.7). On multivariate analysis, baseline MPV >10.1 fL (hazard ratio, 3.20; 95% confidence interval, 1.28–8.03), lesion length (hazard ratio, 1.05; 95% confidence interval, 1.02–1.08), residual stenosis (hazard ratio, 1.07; 95% confidence interval, 1.05–1.10), and baseline glucose (hazard ratio, 1.01; 95% confidence interval, 1.00–1.02) were associated with ISR.

Conclusions—Elevated MPV may be associated with ISR after CAS. Patients with high preprocedural MPV may benefit from an intensified antiplatelet therapy after CAS. **(*Stroke*. 2018;49:872-876. DOI: 10.1161/STROKEAHA.117.019748.)**

Key Words: angioplasty ■ carotid arteries ■ mean platelet volume ■ platelet aggregation ■ stroke

Occlusive lesions in extracranial carotid are responsible for 7% to 20% of ischemic strokes.[1,2] Carotid angioplasty and stenting (CAS) is a valid alternative in treating stenosis in these locations.[3] Compared with carotid endarterectomy, CAS is related to less invasiveness, decreased patient discomfort, and shortened hospitalization.[4] Number of patients with CAS has been increasing since the publication of several large clinical trials that confirmed the effectiveness of this treatment strategy.[5,6] However, the risk–benefit ratio of CAS may be neutralized by late-onset cerebrovascular events related to in-stent restenosis (ISR).[7,8] Exploring the potential influencing factors for ISR, therefore, is of vital importance for continuously improving the efficacy of CAS.

Mean platelet volume (MPV) is regarded as an indicator of platelet reactivity. Larger platelets usually contain more dense granules and pose greater prothrombotic potential.[9] Previous studies have associated elevated MPV with restenosis after coronary angioplasty.[10,11] But the impacts of MPV on restenosis after CAS have not been studied to date. In this study, we assessed the long-term restenosis after CAS by using digital subtraction angiography, computed tomographic angiography, or duplex ultrasonography and then evaluated the impacts of baseline MPV on the development of ISR.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Patients

CAS patients in Nanjing Stroke Registry[12] during December 2005 to November 2016 were enrolled. Ethics approval was obtained from the Ethical Review Board of Jinling Hospital and written informed consent from all patients. Degree of stenosis was determined according to the criteria in NASCET (North American Symptomatic Carotid Endarterectomy trial).[13] CAS was recommended if the patients had ≥50% symptomatic stenoses or ≥70% asymptomatic stenoses in extracranial carotid. CAS was usually detained if the patients (1) had the target stenoses being related to pathogeneses other than atherosclerosis; (2) had concomitant severe heart, lung, kidney diseases or malignant

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tumor; (3) had a life expectancy <5 years; (4) had contraindications for antiplatelet treatment; (5) had major neurological functional impairments or obvious cognitive impairment; (6) had a major stroke within 4 weeks; (7) had severe artery tortuosity or anatomically variant aortic arch which may prevent the safe access of guiding catheter.

Baseline Assessments

Demographic characteristics, presences of major vascular risk factors, and laboratory and imaging results were retrieved from medical records. Before CAS procedures, all patients were treated with dual antiplatelets. In 233 patients, 100 mg aspirin and 75 mg clopidogrel daily were prescribed for at least 7 days. In 28 patients, 100 mg aspirin daily were prescribed for at least 7 days, and 300 mg clopidogrel was prescribed in 4 hours before CAS procedures. In 2 patients who were taking warfarin, dual antiplatelets were also prescribed. After CAS procedures, dual antiplatelets were prescribed for 3 months in patients with warfarin and for 6 month in patients without warfarin. Thereafter, clopidogrel was discontinued and aspirin continued for life time. Venous blood samples were collected within 7 days before CAS procedures and were collected within 7 days after CAS procedures. MPV as well as leukocyte, erythrocyte, and platelet counts were tested by a Sysmex XE-2100 hematology analyzer (Sysmex, Kobe, Japan) within 1 hour of sample collection.

CAS Procedures

The CAS was usually performed under local anesthesia. Body weight–adjusted heparin (70 IU/kg) was given after groin puncture. After the target stenosis being confirmed with an angiography, a 6F or 8F guiding catheter was navigated to the common carotid artery proximal to the stenosis. After a distal embolic protective device being released, a self-expandable stent, such as Precise (Cordis, Miami Lakes, FL), Acculink (Abbott Vascular, Redwood City, CA), or Wallstent (Boston Scientific, Natick, MA), of suitable size was then located and deployed. A complete angiography was performed to identify the residual stenosis immediately after stenting. Pre-dilation were performed in some patients with severe stenoses. Post-dilation were performed in patients with ≥50% residual stenoses.

Follow-Up Assessments

The patients were excluded from the study if they deceased within 30 days of the procedure. Survived patients were followed for clinical outcomes and angiographic changes. Patients were encouraged for a clinical visit whenever a vascular event was indicated. Digital subtraction angiography, computed tomographic angiography, or duplex ultrasonography was performed at 6 months and annually after the procedure. ISR was defined as ≥50% stenosis in the location of target lesion.

Statistical Analysis

Continuous parameters were presented as mean±SD and categorical parameters as number (percentage). The distribution pattern of continuous parameters was checked using Kolmogorov–Smirnov test. Comparisons of multiple mean values were performed by 1-way ANOVA or Kruskal–Wallis *H* test as appropriate. Categorical parameters were tested with χ^2 test and Fisher exact test. Cox regression analysis was used to identify predictors of ISR. Entered factors included those with $P<0.1$ in univariate analysis. Kaplan–Meier analysis was performed to compare cumulative risk of ISR between groups. Time-dependent receiver operating characteristic curve and area under curve were used to evaluate the prediction accuracy of a model.[14] Significance was accepted at $P<0.05$. Statistical analysis was performed using SPSS version 19.0 (SPSS Inc, Chicago, IL) and R version 3.4.3.

Results

A total of 261 patients underwent CAS procedures and survived the first month. The average age of the enrolled patients was 66.5±7.8 (42–86) years. There were 224 (85.8%) men and 37 (14.2%) women. ISR was detected in 46 (17.6%) patients after a mean follow-up of 12.1±16.1 months (range, 2.1–120.7 months; Table 1).

The baseline clinical and biochemical parameters of the enrolled patients were showed according to the tertile of preprocedural MPV (<10.4, tertile 1, n=81; 10.4–11.1, tertile 2, n=91; >11.1, tertile 3, n=89). The 3 groups were comparable, except for the diabetes mellitus ($P=0.037$), symptomatic lesion ($P=0.025$), lesion length ($P=0.013$), lymphocyte ($P=0.007$), platelet ($P<0.001$), C-reactive protein ($P=0.010$), total cholesterol ($P=0.004$), and low-density lipoprotein ($P=0.013$; Table I in the online-only Data Supplement).

Univariate regression analysis showed that diabetes mellitus ($P=0.002$), symptomatic stenosis ($P=0.039$), residual stenosis ($P<0.001$), increased MPV (>10.1 fL; $P=0.021$), and serum glucose ($P<0.001$) were significantly associated with ISR. In addition, length of target lesion ($P=0.06$) and platelet count ($P=0.081$) were marginally associated with ISR. In multivariate Cox analysis, lesion length (hazard ratio, 1.05; 95% confidence interval, 1.02–1.08), residual stenosis (hazard ratio, 1.07; 95% confidence interval, 1.05–1.10), baseline MPV value >10.1 fL (hazard ratio, 3.20; 95% confidence interval, 1.28–8.03), and serum glucose level (hazard ratio, 1.01; 95% confidence interval, 1.00–1.02) were associated with ISR after CAS (Table 2).

The Figure shows the Kaplan–Meier analysis of cumulative freedom from ISR according to MPV value (>10.1 fL or ≤10.1 fL). The log-rank test indicated that risk of ISR was significantly higher in patients with MPV >10.1 fL than patients with MPV ≤10.1 fL at baseline ($P=0.016$). To detect the possibly predictive value of MPV for restenosis, time-dependent receiver operating characteristic curves and area under curve were used to compare the prediction accuracy between the model with and without MPV. Compared with that in the model without MPV, area under curves of 1, 2, and 3 year and average area under curve in the model with MPV improved 8.62%, 2.50%, 5.78%, and 5.63%, respectively (Figure II in the online-only Data Supplement). No significant difference concerning means of MPV before and after CAS was detected (10.89±0.97 versus 10.75±1.11; $P=0.442$; Figure III in the online-only Data Supplement).

Discussion

This study observed that patients with pre-CAS MPV value >10.1 fL had a >3-fold risk of ISR than patients with MPV ≤10.1 fL. To our knowledge, this is the first to identify an association between MPV and ISR after CAS.

ISR has been attributed to neointimal hyperplasia in the early stage after the procedure.[15] Platelets play a central role in neointimal hyperplasia by promoting vascular smooth muscle cell migration and proliferation.[16] Platelet α granules contain platelet-derived growth factor that is both chemotactic and mitogenic for vascular smooth muscle cell.[17] After angioplasty and stenting, platelets may adhere to the site of the injury and release the constituents of α granules, including platelet-derived growth factor.[18] Furthermore, leukocyte–platelet interactions are critical in initiating and promoting

Table 1. Clinical and Biochemical Parameters at Baseline

	All Lesions (n=261)	Restenosis (n=46)	No Restenosis (n=215)	*P* Value
Age, y, mean±SD	66.5±7.8	66.9±6.6	66.4±8.0	0.898
Male, n (%)	224 (85.8)	42 (91.3)	182 (84.7)	0.352
BMI, kg/m^2, mean±SD	24.6±2.9	24.6±2.9	24.6±2.9	0.631
Smoking, n (%)	108 (41.4)	17 (40.0)	91 (42.3)	0.490
Hypertension, n (%)	218 (83.5)	36 (78.3)	182 (84.7)	0.251
Diabetes mellitus, n (%)	99 (37.9)	27 (58.7)	72 (33.5)	0.002
Hyperlipidemia, n (%)	113 (43.3)	18 (39.1)	95 (44.2)	0.131
CAD, n (%)	34 (13.0)	7 (15.2)	27 (12.6)	0.743
Stroke, n (%)	50 (19.2)	13 (28.3)	37 (17.2)	0.348
PAD, n (%)	2 (0.8)	0 (0.0)	2 (0.9)	0.603
Atrial fibrillation, n (%)	7 (2.7)	1 (2.2)	6 (2.8)	0.559
Antithrombotic drugs, n (%)				
Aspirin	29 (11.1)	6 (13.0)	23 (10.7)	0.560
Warfarin	2 (0.8)	0 (0.0)	2 (0.9)	0.546
Symptomatic lesion, n (%)	142 (54.4)	17 (40.0)	125 (58.1)	0.039
Lesion				
Lesion length, mm, mean±SD	20.0±8.6	22.7±9.4	19.4±8.4	0.060
Lesion stenosis, %, mean±SD	79.4±14.5	81.4±13.4	79.0±14.7	0.432
Stenting				
Left carotid, n (%)	134 (51.3)	23 (50.0)	111 (51.6)	0.441
Open cell stent, n (%)	223 (85.4)	41 (89.1)	182(84.7)	0.158
Pre-dilation, n (%)	232 (88.9)	41 (89.1)	191 (88.8)	0.992
Post-dilation, n (%)	69 (26.4)	10 (21.7)	59 (27.4)	0.972
Residual stenosis, %, mean±SD	29.3±10.9	36.6±13.0	27.7±9.7	<0.001
Hematologic parameters				
Leukocyte, ×10^9/L, mean±SD	6.88±1.78	7.10±1.75	6.83±1.79	0.413
Neutrophil, ×10^9/L, mean±SD	4.38±1.56	4.60±1.62	4.33±1.54	0.329
Monocyte, ×10^9/L, mean±SD	0.47±0.15	0.47±0.14	0.47±0.15	0.884
Lymphocyte, ×10^9/L, mean±SD	1.83±0.59	1.82±0.51	1.84±0.61	0.770
Platelet, ×10^9/L, mean±SD	203.1±53.3	191.7±45.7	205.6±54.6	0.081
MPV >10.1 fL, n (%)	196 (75.1)	40 (87.0)	156 (72.6)	0.021
Biochemical parameters				
C-reactive protein, mg/L, mean±SD	5.90±9.31	7.23±12.04	5.61±8.63	0.578
Alanine transaminase, U/L, mean±SD	25.66±16.84	26.42±15.60	25.50±17.12	0.405
Aspartate transaminase, U/L, mean±SD	22.55±10.39	22.05±11.16	22.65±10.24	0.812
Total protein, g/dL, mean±SD	6.64±0.53	6.66±0.46	6.64±0.55	0.713
Albumin, g/dL, mean±SD	4.25±0.37	4.23±0.37	4.25±0.37	0.231
Globulin, g/dL, mean±SD	2.40±0.41	2.43±0.38	2.39±0.42	0.555
Creatinine, mg/dL, mean±SD	0.82±0.21	0.83±0.20	0.82±0.22	0.552
Uric acid, mg/dL, mean±SD	5.33±1.42	5.28±1.31	5.34±1.44	0.653
Serum glucose, mg/dL, mean±SD	102.3±33.02	113.2±51.08	100.0±27.30	<0.001
Total cholesterol, mg/dL, mean±SD	154.5±40.37	152.7±36.78	154.9±41.17	0.899
Triglyceride, mg/dL, mean±SD	135.0±84.92	127.4±57.69	136.7±89.70	0.669
HDL, mg/dL, mean±SD	39.40±8.37	39.69±10.49	39.34±7.88	0.949
LDL, mg/dL, mean±SD	92.17±33.08	88.54±31.20	92.95±33.49	0.460

BMI indicates body mass index; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MPV, mean platelet volume; and PAD, Peripheral arterial disease.

Table 2. Multivariate Analysis of Predictors of ISR After Carotid Artery Stenting

	Multivariate HR (95% CI)	*P* Value
Diabetes mellitus	1.03 (0.52–2.06)	0.923
Symptomatic lesion	0.62 (0.32–1.21)	0.161
Lesion length	1.05 (1.02–1.08)	0.002
Residual stenosis	1.07 (1.05–1.10)	<0.001
Platelet	1.00 (0.99–1.00)	0.187
MPV >10.1 fL	3.20 (1.28–8.03)	0.013
Serum glucose	1.01 (1.00–1.02)	0.003

CI indicates confidence interval; HR, hazard ratio; ISR, in-stent restenosis; and MPV, mean platelet volume.

neointimal hyperplasia.[19] Inflammatory cells may accelerate neointimal hyperplasia because of their release of growth and chemotactic factors[20] or production of enzymes (eg, matrix metalloproteinases), which can degrade extracellular constituents and facilitate cell migration.[21,22]

The relationship between MPV and ISR after CAS may be explained with 3 possible mechanisms. First, an increased MPV level has been considered as a marker of greater platelet size and activity. Larger platelets contain more platelet granules and thereby increased the platelet-derived growth factor levels at the injured site. Therefore, higher MPV levels may pose patients with increased potential for neointimal hyperplasia. Second, mechanical lesions of arterial endothelium may activate platelets and recruit leukocyte to the injury. Leukocyte–platelet interactions can lead to inflammatory response that aggravates neointimal hyperplasia. Inflammatory response may be further aggravated in patients with higher MPV because of more intensive platelet activation. Finally, an elevated MPV value may reflect an increase in reticulated platelets or immature platelets, which is an indicator of platelet turnover. It has been reported that high platelet turnover is associated with platelet aggregation and lower response to antiplatelet therapy.[23,24]

In addition, this study showed that lesion length and residual stenosis were significantly associated with ISR after CAS. Our findings are in agreement with the results in several studies of risk factors for ISR.[25–27] Residual stenosis is a risk factor of restenosis, and it conflicts with the opinion that a perfect angiographic result after CAS is not necessary.[28] Considering the increasing risk of embolization and neointimal proliferation by high postdilation pressures,[29] the pre-dilation may be an effective measure to eliminate the residual stenosis as much as possible.

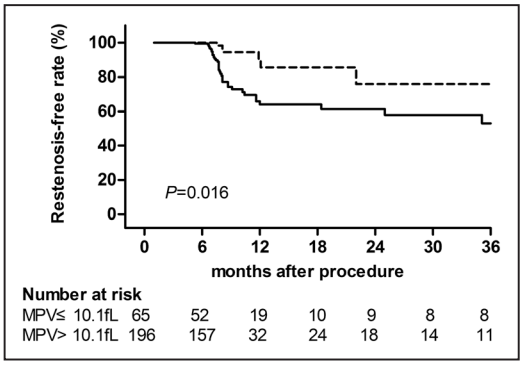

Figure. Cumulative freedom from in-stent restenosis with Kaplan–Meier analysis. Patients with mean platelet volume (MPV) ≤10.1 fL were displayed with dotted line; Patients with MPV >10.1 fL were displayed with solid line. Cumulative rates of freedom from in-stent restenosis were compared with log-rank test.

In this study, MPV was not significantly influenced by CAS procedure and short-term antiplatelet treatment. A few studies reported the effects of antiplatelets on MPV, and inconsistent results were reported.[30–32] One study reported that MPV were not affected by 1-week low-dose aspirin treatment.[31] Another study of small samples reported that MPV was reduced after 4-week antiplatelet treatment.[32] These results suggested that intensified and prolonged antiplatelet treatment may reduce MPV.

Some limitations should be emphasized when interpreting the results of this study. We did not consider the effect of some drugs before and after the procedure in the study. Previous studies indicate that antihypertensive,[33] lipid-lowing,[34] and antidiabetic[35] drugs may influence MPV value. Further studies are warranted to confirm the impacts of MPV on ISR.

Conclusions

Elevated MPV may be associated with ISR after CAS. Patients with high preprocedural MPV may benefit from an intensified antiplatelet therapy after CAS.

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Disclosures

None.

References

1. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/ CNS/SAIP/SCAI/ SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease. *Stroke*. 2011;42:e464–e540. doi: 10.1161/STR.0b013e3182112cc2.
2. Chaturvedi S, Sacco RL. How recent data have impacted the treatment of internal carotid artery stenosis. *J Am Coll Cardiol*. 2015;65:1134–1143. doi: 10.1016/j.jacc.2014.12.045.
3. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160–2236. doi: 10.1161/STR.0000000000000024.
4. Cohen DJ, Stolker JM, Wang K, Magnuson EA, Clark WM, Demaerschalk BM, et al; CREST Investigators. Health-related quality of life after carotid stenting versus carotid endarterectomy: results from CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial). *J Am Coll Cardiol*. 2011;58:1557–1565. doi: 10.1016/j.jacc.2011.05.054.
5. McDonald JS, McDonald RJ, Fan J, Lanzino G, Kallmes DF, Cloft HJ. Effect of CREST findings on carotid revascularization practice in the United States. *J Stroke Cerebrovasc Dis*. 2015;24:1390–1396. doi: 10.1016/j.jstrokecerebrovasdis.2015.02.020.
6. Hussain MA, Mamdani M, Tu JV, Saposnik G, Khoushhal Z, Aljabri B, et al. Impact of clinical trial results on the temporal trends of carotid endarterectomy and stenting from 2002 to 2014. *Stroke*. 2016;47:2923–2930. doi: 10.1161/STROKEAHA.116.014856.

7. Lal BK, Beach KW, Roubin GS, Lutsep HL, Moore WS, Malas MB, et al; CREST Investigators. Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomised controlled trial. *Lancet Neurol*. 2012;11:755–763. doi: 10.1016/S1474-4422(12)70159-X.
8. Zapata-Arriaza E, Moniche F, González A, Bustamante A, Escudero-Martínez I, De la Torre Laviana FJ, et al. Predictors of restenosis following carotid angioplasty and stenting. *Stroke*. 2016;47:2144–2147. doi: 10.1161/STROKEAHA.116.012650.
9. Kamath S, Blann AD, Lip GY. Platelet activation: assessment and quantification. *Eur Heart J*. 2001;22:1561–1571. doi: 10.1053/euhj.2000.2515.
10. Norgaz T, Hobikoglu G, Aksu H, Bolca O, Uyarel H, Eren M, et al. The relationship between preprocedural platelet size and subsequent in-stent restenosis. *Acta Cardiol*. 2004;59:391–395. doi: 10.2143/AC.59.4.2005204.
11. Yang A, Pizzulli L, Luderitz B. Mean platelet volume as marker of restenosis after percutaneous transluminal coronary angioplasty in patients with stable and unstable angina pectoris. *Thromb Res*. 2006;117:371–377. doi: 10.1016/j.thromres.2005.04.004.
12. Liu X, Xu G, Wu W, Zhang R, Yin Q, Zhu W. Subtypes and one-year survival of first-ever stroke in Chinese patients: the Nanjing Stroke Registry. *Cerebrovasc Dis*. 2006;22:130–136. doi: 10.1159/000093241.
13. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 1998;339:1415–1425. doi: 10.1056/NEJM199811123392002.
14. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics*. 2000;56:337–344.
15. Goel SA, Guo LW, Liu B, Kent KC. Mechanisms of post-intervention arterial remodelling. *Cardiovasc Res*. 2012;96:363–371. doi: 10.1093/cvr/cvs276.
16. Mitra AK, Agrawal DK. In stent restenosis: bane of the stent era. *J Clin Pathol*. 2006;59:232–239. doi: 10.1136/jcp.2005.025742.
17. Ross R. The pathogenesis of atherosclerosis–an update. *N Engl J Med*. 1986;314:488–500. doi: 10.1056/NEJM198602203140806.
18. Goldberg ID, Stemerman MB, Handin RI. Vascular permeation of platelet factor 4 after endothelial injury. *Science*. 1980;209:611–612.
19. Simon DI, Dhen Z, Seifert P, Edelman ER, Ballantyne CM, Rogers C. Decreased neointimal formation in Mac-1(-/-) mice reveals a role for inflammation in vascular repair after angioplasty. *J Clin Invest*. 2000;105:293–300. doi: 10.1172/JCI7811.
20. Assoian RK, Fleurdelys BE, Stevenson HC, Miller PJ, Madtes DK, Raines EW, et al. Expression and secretion of type beta transforming growth factor by activated human macrophages. *Proc Natl Acad Sci USA*. 1987;84:6020–6024.
21. Garbisa S, Ballin M, Daga-Gordini D, Fastelli G, Naturale M, Negro A, et al. Transient expression of type IV collagenolytic metalloproteinase by human mononuclear phagocytes. *J Biol Chem*. 1986;261:2369–2375.
22. Sukhova GK, Shi GP, Simon DI, Chapman HA, Libby P. Expression of the elastolytic cathepsins S and K in human atheroma and regulation of their production in smooth muscle cells. *J Clin Invest*. 1998;102:576–583. doi: 10.1172/JCI181.
23. Grove EL, Hvas AM, Mortensen SB, Larsen SB, Kristensen SD. Effect of platelet turnover on whole blood platelet aggregation in patients with coronary artery disease. *J Thromb Haemost*. 2011;9:185–191. doi: 10.1111/j.1538-7836.2010.04115.x.
24. Guthikonda S, Alviar CL, Vaduganathan M, Arikan M, Tellez A, DeLao T, et al. Role of reticulated platelets and platelet size heterogeneity on platelet activity after dual antiplatelet therapy with aspirin and clopidogrel in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2008;52:743–749. doi: 10.1016/j.jacc.2008.05.031.
25. Shankar JJ, Zhang J, dos Santos M, Lesiuk H, Mohan R, Lum C. Factors affecting long-term restenosis after carotid stenting for carotid atherosclerotic disease. *Neuroradiology*. 2012;54:1347–1353. doi: 10.1007/s00234-012-1031-y.
26. Cosottini M, Michelassi MC, Bencivelli W, Lazzarotti G, Picchietti S, Orlandi G, et al. In stent restenosis predictors after carotid artery stenting. *Stroke Res Treat*. 2010;2010:864724. doi: 10.4061/2010/864724.
27. Schillinger M, Exner M, Mlekusch W, Rumpold H, Ahmadi R, Sabeti S, et al. Acute-phase response after stent implantation in the carotid artery: association with 6-month in-stent restenosis. *Radiology*. 2003;227:516–521. doi: 10.1148/radiol.2272020183.
28. Bates ER, Babb JD, Casey DE Jr, Cates CU, Duckwiler GR, Feldman TE, Gray WA, et al; American College of Cardiology Foundation; American Society of Interventional & Therapeutic Neuroradiology; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society of Interventional Radiology. ACCF/SCAI/SVMB/SIR/ASITN 2007 clinical expert consensus document on carotid stenting: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (ACCF/SCAI/SVMB/SIR/ASITN Clinical Expert Consensus Document Committee on Carotid Stenting). *J Am Coll Cardiol*. 2007;49:126–170. doi: 10.1016/j.jacc.2006.10.021.
29. Han RO, Schwartz RS, Kobayashi Y, Wilson SH, Mann JT, Sketch MH, et al; Stent Comparative Restenosis (SCORES) Trial Investigators. Comparison of self-expanding and balloon-expandable stents for the reduction of restenosis. *Am J Cardiol*. 2001;88:253–259.
30. De Luca G, Secco GG, Iorio S, Verdoia M, Bellomo G, Marino P. Short-term effects of aspirin and clopidogrel on mean platelet volume among patients with acute coronary syndromes. A single-center prospective study. *Blood Coagul Fibrinolysis*. 2012;23:756–759. doi: 10.1097/MBC.0b013e328358e941.
31. Shah B, Valdes V, Nardi MA, Hu L, Schrem E, Berger JS. Mean platelet volume reproducibility and association with platelet activity and anti-platelet therapy. *Platelets*. 2014;25:188–92. doi: 10.3109/09537104.2013.793794.
32. Haungsaithong R, Udommongkol C, Nidhinandana S, Chairungsaris P, Chinvarun Y, Suwantamee J, et al. The changes in mean platelet volume after using of antiplatelet drugs in acute ischemic stroke: a randomized controlled trial. *J Med Assoc Thai*. 2015;98:852–857.
33. Nadar S, Blann AD, Lip GY. Platelet morphology and plasma indices of platelet activation in essential hypertension: effects of amlodipine-based antihypertensive therapy. *Ann Med*. 2004;36:552–557. doi: 10.1080/07853890410017386.
34. Akyuz A, Akkoyun DC, Degirmenci H, Oran M. Rosuvastatin decreases mean platelet volume in patients with diabetes mellitus. *Angiology*. 2016;67:116–120. doi: 10.1177/0003319715584725.
35. Sertbas Y, Sertbas M, Okuroglu N, Ozturk MA, Abacar KY, Ozdemir A. Mean platelet volume changes before and after glycated hemoglobin (HbA1c) improvement in a large study population. *Arch Med Sci*. 2017;13:711–715. doi: 10.5114/aoms.2016.61900.