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Letter to the Editors-in-Chief

No independent association found between von Willebrand factor and plaque ulceration in carotid artery atherosclerosis

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Atherosclerotic plaque development starts with endothelial dysfunction, which leads to intimal thickening that finally ends in lipid accumulation beneath a fibrous cap, and formation of calcifications [1]. Atherosclerotic plaques with a specific morphologic buildup of plaque components, the so-called vulnerable plaque, are mechanically unstable, which can lead to plaque rupture. Carotid plaque rupture can lead to platelet aggregation, thrombus formation and embolization of thrombus and/or plaque material into the distal intracranial arteries, which causes an ischemic stroke [2]. Previous studies have shown a strong correlation between carotid artery plaque ulceration and histologic characteristics of plaque instability, such as intraplaque hemorrhage and plaque rupture [3]. New accurate imaging techniques like Computed Tomography Angiography (CTA) and Magnetic Resonance Imaging (MRI) can identify atherosclerotic plaque composition, such as lipid-rich necrotic core, intraplaque hemorrhage and calcifications with a high accuracy. In addition, plaque ulceration, which is an independent predictor of ischemic stroke, can be detected with CTA and MRI as well [4].

von Willebrand Factor (VWF) is a plasma glycoprotein, which is involved in platelet adhesion and leads to thrombus formation. An increased level of VWF is seen as a result of adverse changes to endothelium and is associated with an increased risk of ischemic stroke [5]. It is yet unknown whether atherosclerotic plaque leads to changes in hemostasis with a subsequent increase in ischemic stroke risk or whether atherosclerotic plaque and hemostatic changes independently increase ischemic stroke risk. In a previous study we evaluated the association between degree of calcification volume and VWF levels, and concluded that extent of calcification volumes in the carotid arteries and aortic arch are strongly associated with VWF levels [6]. As plaque ulceration is considered as an important step in the pathophysiology of ischemic stroke, we investigated whether there is a relationship between plaque ulceration in the carotid artery and VWF levels in patients with ischemic stroke.

In the current study we included 985 patients with acute transient ischemic attack (TIA) or ischemic stroke who were evaluated between July 2005 and November 2010 and had undergone blood sampling, genotyping and a CTA of the carotid bifurcation. All participants provided written informed consent. The study was approved by the Medical Ethics Committee of the Erasmus MC. Baseline characteristics have been described previously [6]. Stroke was classified by subtypes by using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, at admission at the stroke unit or at the outpatient clinic [7].

Imaging was performed with a 16, 64 or 128 slice multidetector CT scanner. Calcification volume in the carotid arteries was quantified as described previously [6]. The average calcification volume of both carotid arteries was used. Both carotid arteries were evaluated for presence of plaque ulceration, defined as extension of contrast material of > 1 mm in the surrounding atherosclerotic plaque on at least two orthogonal planes [8]. Ulceration was scored as present if one of the carotid arteries showed a plaque ulceration. The degree of carotid artery stenosis was measured in both arteries, according to the ECST criteria. The most severe stenosis was used for analysis.

Patients were subjected to blood sampling approximately 6 days after onset of symptoms (interquartile range 3–14 days) and VWF:Ag levels were determined [6].

The distributions of VWF levels and calcification volumes in the carotid arteries were normalized by logarithmic transformation. For the analysis of calcification volume, we added 1.0 mm^3 to the non-transformed values to deal with participants with a calcification volume of zero. Multiple imputation was used to deal with the missing data of BMI. Linear regression analysis was used to analyze the relationship between ulceration, calcification volume and cardiovascular risk factors and VWF levels. Model I was adjusted for age, sex and ABO blood group. Model II was additionally adjusted for calcification volume, and for cardiovascular risk factors with a p value < 0.05 in model I. In model III we only adjusted for blood group and calcification volume. All analyses were performed using SPSS version 21.0 (IBM, Somers, NY, USA). A p value < 0.05 was considered to indicate statistical significance.

21 of the 985 patients were excluded due to lack of information about the carotid bifurcation, as a result of missing CTA (n = 12), major artifacts (n = 7) or poor contrast enhancement (n = 2).

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Table 1
Determinants of von Willebrand factor.

Characteristics	Model I[a] beta [95% CI]	p value	Model II[b] beta [95% CI]	p value	Model III[c] beta [95% CI]	p value
Age, years	0.008 [0.007; 0.010]	< 0.001	0.005 [0.003; 0.007]	0.000	0.006 [0.004; 0.008]	0.000
Female	0.048 [−0.002; 0.098]	0.062	–	–	0.026 [−0.022; 0.074]	0.293
Body mass index (kg/m^2)	0.001 [−0.001; 0.004]	0.329	–	–	0.001 [0.001–0.002]	0.000
Hypertension	0.080 [0.028; 0.133]	0.003	0.044 [−0.007; 0.095]	0.090	0.083 [0.033; 0.133]	0.001
Hypercholesterolemia	0.049 [−0.004; 0.103]	0.072	–	–	0.034 [−0.018; 0.085]	0.204
Diabetes mellitus	0.074 [0.002; 0.145]	0.044	0.047 [−0.021; 0.114]	0.175	0.049 [−0.019; 0.118]	0.160
History of CVD	0.010 [−0.044; 0.064]	0.716	–	–	0.020 [−0.031; 0.072]	0.440
Current smoking	0.010 [−0.046; 0.066]	0.735	–	–	−0.047 [−0.100; 0.005]	0.078
Blood group O	−0.266 [−0.313; −0.218]	0.000	−0.264 [−0.311; −0.217]	0.000	−0.271 [0.319; 0.222]	0.000
TOAST classification						
Large artery atherosclerosis	0.133 [0.066; 0.200]	0.000	0.079 [−0.039; 0.197]	0.190	0.096 [0.030; 0.162]	0.005
Cardio-embolism	0.081 [0.004; 0.159]	0.040	0.057 [−0.065; 0.178]	0.361	0.073 [0.000; 0.146]	0.051
Small vessel occlusion	−0.081 [−0.143; −0.018]	0.012	−0.071 [−0.184; 0.042]	0.217	−0.085 [−0.145; −0.124]	0.006
Undetermined	−0.054[−0.105; 0.004]	0.035	−0.014[−0.119; 0.092]	0.798	−0.017 [−0.065; 0.031]	0.491
Carotid plaque ulceration	0.066 [0.003; 0.129]	0.040	0.027 [−0.036; 0.089]	0.403	0.060 [−0.003; 0.123]	0.060
Calcification volume (mm^3)	0.067 [0.041; 0.092]	0.000	0.053 [0.028; 0.079]	0.000	0.059 [0.046; 0.072]	0.000
Degree of stenosis (%)	0.000 [0.000; 0.001]	0.383			0.001 [0.000; 0.002]	0.012

[a] Adjusted for age and sex.
[b] Adjusted for age, sex, blood group, calcification volume and all cardiovascular risk factors with p value < 0.05 in model I.
[c] Adjusted for blood group and calcification volume.

Mean age at baseline was 62 ± 14 year and 46% of the patients were female. Mean VWF:Ag levels were 1.6 ± 0.7 IU/ml. Plaque ulceration was seen in 7% (136/1928) of the carotid arteries and in 13% (128/964) of the patients. Plaque calcifications were present in 48% (920/1928) of the carotid arteries with a median volume of 1.68 ± 1.89 mm^3. Most severe degree of carotid artery stenosis was 100%, with a median of 0 [0–56].

The determinants of VWF levels are presented in Table 1. A significant correlation was seen between plaque ulceration and VWF levels, after correction for age and sex (β = 0.066 [0.003–0.129]; p = 0.040). After additional adjustment for blood group, calcification volume and all cardiovascular risk factors with p value < 0.05 plaque ulceration was not significant associated with VWF levels (β = 0.027 [−0.036–0.089]; p = 0.403). After adjustment for blood group and calcification volume only (model III), plaque ulceration was not significant associated with VWF levels (β = 0.060 [−0.003–0.123]; p = 0.060). Reanalysis in the patients with large artery atherosclerosis revealed no association between plaque ulceration and VWF levels.

In the current study we evaluated whether plaque ulceration was related to an increased VWF level. Our findings showed no independent correlation between plaque ulceration and increased VWF levels after adjustment for age, sex, blood group and calcification volume.

Previous studies have demonstrated a strong correlation between ischemic stroke and higher VWF levels [5]. Lip et al. has shown that a high level of VWF has a prognostic value in patients with ischemic heart disease and inflammatory vascular disease. However, there is limited evidence that a higher level of VWF induces progression of vascular diseases [9]. Wieberdink et al. studied the correlation between the risk of stroke and VWF levels in the general population, and found a significant correlation also after adjustment for additional confounders [10]. This supports the hypothesis that VWF levels could be an index of endothelial damage in vascular disease.

As high VWF levels increases the risk of ischemic stroke [5], the question arises whether atherosclerotic plaque leads to changes in hemostasis and a subsequent increased risk of ischemic stroke, or whether both atherosclerotic plaque and hemostatic changes independently increase risk of ischemic stroke. The absence of an association between plaque ulceration and VWF levels after adjustment for calcifications does not support the hypothesis that VWF levels are affected by the presence of plaque ulceration and that a higher level of VWF an intermediate risk factor is in the pathway between atherosclerotic disease and ischemic stroke.

A limitation of our study is that patients with significant comorbidity, very severe stroke or those who died within 24 h, were not included in this study. This resulted in a relatively less severely affected cohort and as a result less patients with ulcerations are included in this study resulting in dilution of a possible association.

In conclusion, atherosclerotic plaque ulceration in the carotid arteries is not, independently of calcification volume, related to higher levels of VWF in patients with TIA or ischemic stroke.

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Conflict of interest

None.

Disclosures

None.

References

[1] A.V. Finn, F.D. Kolodgie, R. Virmani, Correlation between carotid intimal/medial thickness and atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 30 (2010) 177–181.
[2] G.A. Lammie, P.A. Sandercock, M.S. Dennis, Recently occluded intracranial and extracranial carotid arteries. Relevance of the unstable atherosclerotic plaque, Stroke 30 (1999) 1319–1325.
[3] J.K. Lovett, P.J. Gallagher, L.J. Hands, J. Walton, P.M. Rothwell, Histological correlates of carotid plaque surface morphology on lumen contrast imaging, Circulation 110 (2004) 2190–2197.
[4] P.M. Rothwell, R. Gibson, C.P. Warlow, Interrelation between plaque surface morphology and degree of stenosis on carotid angiograms and the risk of ischemic stroke in patients with symptomatic carotid stenosis. On behalf of the European Carotid Surgery Trialists' Collaborative Group, Stroke 31 (2000) 615–621.
[5] T.N. Bongers, M. de Maat, M.L. van Goor, V. Bhagwanbali, H.H. van Vliet, E.B. Gómez García, et al., High von Willebrand factor levels increase the risk of first ischemic stroke: influence of adamts13, inflammation, and genetic variability, Stroke 37 (2006) 2672–2677.
[6] M.A. Sonneveld, A.C. van Dijk, E.G. van den Herik, J.E. van Loon, L.M. de Lau, A. van der Lugt, et al., Relationship of von Willebrand factor with carotid artery and aortic arch calcification in ischemic stroke patients, Atherosclerosis 230 (2013) 210–215.

[7] H.P. Adams Jr., P.H. Davis, E.C. Leira, K.C. Chang, B.H. Bendixen, W.R. Clarke, et al., Baseline NIH stroke scale score strongly predicts outcome after stroke: a report of the trial of org 10172 in acute stroke treatment (TOAST), Neurology 53 (1999) 126–131.
[8] T.T. de Weert, S. Cretier, H.C. Groen, P. Homburg, H. Cakir, J.J. Wentzel, et al., Atherosclerotic plaque surface morphology in the carotid bifurcation assessed with multidetector computed tomography angiography, Stroke 40 (2009) 1334–1340.
[9] G.Y. Lip, A. Blann, von Willebrand factor: a marker of endothelial dysfunction in vascular disorders? Cardiovasc. Res. 34 (1997) 255–265.
[10] R.G. Wieberdink, M.C. van Schie, P.J. Koudstaal, A. Hofman, J.C. Witteman, M.P. de Maat, et al., High von Willebrand factor levels increase the risk of stroke: the Rotterdam study, Stroke 41 (2010) 2151–2156.

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