Impact of von Willebrand factor on coronary plaque burden in coronary artery disease patients treated with statins

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Abstract
High von Willebrand factor (VWF) levels have been reported to be associated with an increased risk of cardiovascular events. However, the relationship between VWF levels and coronary atherosclerosis in patients with coronary artery disease (CAD) who have already received statin treatment is still unclear. We examined the association between VWF levels and coronary plaque as assessed by intravascular ultrasound (IVUS) in CAD patients treated with statins. Ninety-one CAD patients who underwent percutaneous coronary intervention under IVUS guidance, and who were already receiving statin treatment based on Japanese guidelines, were included. An IVUS examination was performed for the culprit lesion, and plasma VWF antigen levels were measured using enzyme-linked immuno sorbent assay. In all of the patients, the low-density lipoprotein cholesterol levels just before the IVUS examination were low (86 ± 26 mg/dL). The VWF levels were positively correlated with the plaque burden expressed as percent atheroma volume (PAV) (r = 0.30, P = .004), while there was no significant association between VWF and plaque composition. Multivariate stepwise regression analysis showed that higher VWF levels were independently associated with increased PAV (β = 0.26, P = .01). In CAD patients who had already been treated with statins, higher VWF levels were associated with a higher coronary plaque burden, suggesting that a high VWF level may be a marker of the residual cardiovascular risk after statin treatment.

Abbreviations: ACS = acute coronary syndrome, AF = atrial fibrillation, CAD = coronary artery disease, CSA = cross-sectional area, EEM = external elastic membrane, eGFR = estimated glomerular filtration rate, ELISA = enzyme-linked immuno sorbent assay, HDL-C = high-density lipoprotein cholesterol, hs-CRP = high-sensitivity C-reactive protein, IB = integrated backscatter, IVUS = intravascular ultrasound, LDL-C = low-density lipoprotein cholesterol, NO = nitric oxide, OACs = oral anticoagulants, PAV = percent atheroma volume, PCI = percutaneous coronary intervention, VWF = von Willebrand factor.

Keywords: coronary atherosclerosis, coronary plaque, intravascular ultrasound, von Willebrand factor

1. Introduction
von Willebrand factor (VWF) is a glycoprotein that is produced mainly by vascular endothelial cells in humans. VWF mediates platelet adhesion and aggregation, and plays a crucial role in primary hemostasis and the initial steps in thrombus formation. VWF levels are considered to increase as a result of vascular endothelial damage, and VWF may be a marker of vascular injury. In addition, high VWF levels have been reported to be associated with an increased risk of cardiovascular events. Statin is a standard treatment for the prevention of cardiovascular diseases and has favorable pleiotropic effects on atherosclerosis. However, cardiovascular events continue to occur at an unacceptable frequency in patients who are receiving statins. We hypothesized that a high VWF level may be a marker of the residual cardiovascular risk after statin treatment.

Intravascular ultrasound (IVUS) is an imaging modality that enables the precise quantification of coronary atherosclerosis. The IVUS-derived coronary atheroma burden is considered to be a useful marker of the risk of cardiovascular events even in patients who are receiving statin therapy. At present, little is known about the association between the level of VWF and coronary plaque as assessed by IVUS. Therefore, to elucidate whether VWF is a marker of the residual cardiovascular risk after statin treatment, we examined the relationship between VWF levels and coronary plaque using IVUS in coronary artery disease (CAD) patients who had been treated with statins.

2. Materials and methods

2.1. Patients and study design
A total of 1271 patients with CAD who underwent percutaneous coronary intervention (PCI) at Fukuoka University Hospital from
February 2012 to January 2016 were screened according to the following exclusion criteria: patients who did not undergo IVUS-guided PCI; blood disease (e.g., von Willebrand disease); familial hypercholesterolemia; liver cirrhosis; severe infection; recent surgery or trauma; and contraindication to antiplatelet agents or statins. Of these, 153 patients in whom we could obtain consent for measurement of the VWF level were included. We also excluded 44 patients who had not received statins before PCI, 5 patients with acute coronary syndrome (ACS) and 13 patients with unanalyzable IVUS images. Ultimately, 91 stable CAD patients who had already received statin therapy before IVUS-guided PCI were included in this study.

According to the Japanese guidelines for the secondary prevention of myocardial infarction, all of the patients received a standard antiplatelet therapy (aspirin and thienopyridines) before PCI. Statin treatment was based on the Japan Atherosclerosis Society guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases, and the target level of low-density lipoprotein cholesterol (LDL-C) was <100 mg/dL. Fasting blood samples for the measurement of clinical laboratory data, including plasma levels of VWF and high-sensitivity C-reactive protein (hs-CRP), were obtained just before PCI.

This study was approved by the ethics committee of Fukuoka University Hospital (EC/IRB: 15-3-12) and conducted according to the Declaration of Helsinki regarding investigations in humans.

2.2. IVUS procedure and analysis

Before IVUS-guided PCI, IVUS examination was performed for the culprit lesion of a coronary artery using an imaging catheter and a console (View IT and VISIWAVE, Terumo, Tokyo, Japan) (Fig. 1). An optimal dose of nitroglycerin was injected into the coronary artery just before IVUS examination to prevent coronary spasm. The IVUS catheter was advanced to the distal side of the culprit lesion and pulled back automatically at a speed of 0.5 mm/sec.

For IVUS analysis, first, the cross-section with the smallest minimum lumen area of the culprit lesion was identified. Next, the cross-sections that were located 5 mm proximal and distal to the most diseased cross-section were identified. This process identified the 10 mm segment that was considered for IVUS analysis (Fig. 1). IVUS analysis of the culprit lesion was conducted using an integrated backscatter (IB) IVUS analysis system (VISIATLAS, Terumo, Tokyo, Japan), which measures both plaque volume and plaque composition. This system has been reported to be comparable to a commonly used IVUS analysis system (echoPlaque, INDEC Systems, Santa Clara, CA) and to have excellent reliability and validity. External elastic membrane (EEM) cross-sectional area (CSA) and lumen CSA were manually traced at 1-mm axis intervals for a length of 10 mm (Fig. 1), and atheroma CSA (EEM CSA minus lumen CSA) was calculated. The remodeling index was calculated as the EEM CSA of the lesion site divided by the average EEM CSA of the proximal and distal reference sites. The lesion length of the culprit lesion was calculated as the distance between the proximal and distal reference sites using the above-mentioned IVUS analysis system. Vessel volume and lumen volume were calculated automatically as $\Sigma$ EEM CSA and $\Sigma$ lumen CSA, respectively. Total atheroma volume and percent atheroma volume (PAV) were calculated as follows:

$$\text{Total atheroma volume} = \Sigma \text{EEM CSA} - \Sigma \text{lumen CSA}$$

$$\text{PAV} = \frac{100 \times \text{total atheroma volume}}{\Sigma \text{EEM CSA}}$$

Figure 1. Representative coronary angiogram of the evaluated vessel for IVUS analysis. The target segment for IVUS analysis included the most-diseased cross-section before PCI, and its length was 10 mm. IVUS = intravascular ultrasound, PCI = percutaneous coronary intervention.
The tissue characteristics of coronary plaque were analyzed by the software for IB IVUS that came with the above-mentioned IVUS analysis system. The plaque components were divided into 4 classifications: lipid, fibrosis, dense fibrosis, and calcification, as reported previously.14 The area and volume of each plaque classification were calculated automatically and presented as percentages.

IVUS analysis was performed by an experienced physician who was unaware of the patient characteristics according to the criteria described in the American College of Cardiology Clinical Expert Consensus document of IVUS.10

2.3. Clinical laboratory examinations

Serum levels of LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglyceride, serum creatinine level, fasting blood sugar, hemoglobin A1C level, and uric acid level were measured at the Fukuoka University Hospital Laboratory Unit. Estimated glomerular filtration rate (eGFR) was calculated as follows: 194 × serum creatinine−0.57 × age−0.33 (male), 194 × serum creatinine−0.66 × age−0.167 × 0.739 (female). The blood samples for the measurement of VWF and hs-CRP levels were prepared by centrifugation (20 minutes at 3000 rpm at 4°C) and stored at −80°C until use. Plasma levels of VWF (VWF antigen levels) and hs-CRP were measured at SRL Co Lt. (Tokyo, Japan). For the measurement of VWF levels, enzyme-linked immunosorbent assay (ELISA) microplates (STA-LIATEST VWF:Ag, DIAGNOSTICA STAGO S.A.S, Paris, France) were used.17

2.4. Statistical data analysis

The SAS software package (version 9.4, SAS Institute) at Fukuoka University (Fukuoka, Japan) was used for statistical data analyses. Categorical variables are presented as numbers (%), and continuous variables are presented as mean ± SD or median [interquartile range (IQR, 25th–75th percentile)]. Univariate regression analysis was performed to evaluate the correlation between continuous variables including the VWF level and IVUS parameters. To identify the factors that were associated with the coronary plaque burden presented as PAV, a multivariate stepwise regression analysis was conducted among conventional risk factors (age, gender, body mass index, current smoking, hypertension, and diabetes mellitus), LDL-C and VWF level. A P value of < 0.05 was considered to indicate statistical significance unless indicated otherwise.

3. Results

3.1. Characteristics of the patients and clinical laboratory data

Table 1 shows the patient characteristics in this study. The mean age was 70 ± 8 years, and 66 of the patients were male (73%). The frequencies of hypertension, diabetes, and dyslipidemia were 85%, 75% and 90%, respectively. The frequency of paroxysmal, persistent, or permanent atrial fibrillation (AF) was 10%, and all of the patients with AF were already being treated with oral anticoagulants (OACs). All of the patients in this study were already receiving statin and dual antplatelet therapy (aspirin and thienopyridines) before PCI and IVUS examination.

Table 2 shows the clinical laboratory data for the subjects in this study. Lipid profiles were well controlled according to the Japanese guidelines; serum LDL-C levels were low (86 ± 26 mg/dL), and HDL-C and triglyceride levels were 47 ± 12 mg/dL and 138 ± 73 mg/dL, respectively. Systolic and diastolic blood pressure were 128 ± 18 mm Hg and 70 ± 12 mm Hg, respectively.

3.2. Gray-scale and IB IVUS parameters at the culprit lesion

Gray-scale and IB IVUS parameters at the culprit lesion are summarized in Table 3. In the most diseased cross-section, the lumen area and the percentage of plaque area were 1.9 ± 0.5 mm² and 81 ± 7%, respectively. The lesion length was 15.7 ± 7.7 mm, and the remodeling index was 0.96 ± 0.19. The percent atheroma volume was 68 ± 12%, and the percentages of lipid volume and fibrous volume were 56 ± 16% and 36 ± 11%, respectively.

3.3. Associations between clinical data and coronary plaque

Figure 2 shows the associations between VWF levels and IVUS parameters as assessed by univariate regression analysis. While VWF levels were positively correlated with PAV (r = 0.34, P = 0.003) (Fig. 2A), there was no significant association between VWF and plaque composition (Fig. 2B–E).

Table 4 shows the results of a univariate regression analysis to identify the factors associated with PAV at the culprit lesion. While the VWF level was significantly associated with PAV (r =
0.39, \(P=0.001\), age, male gender, body mass index, hypertension, diabetes mellitus, current smoking, LDL-C, HDL-C, triglyceride, eGFR, uric acid and hs-CRP were not. A multivariate stepwise regression analysis indicated that VWF levels (\(b=0.26, P=0.01\)) was independently associated with PAV (Table 5).

4. Discussion

The main finding of this study was that higher VWF levels were significantly associated with a higher coronary plaque burden in CAD patients who had already received statin treatment (Fig. 2A, Tables 4 and 5).

VWF is produced almost exclusively by vascular endothelial cells\(^{[2,18]}\) and mediates platelet adhesion and aggregation.\(^{[1]}\) VWF and platelets play important roles in the initiation of atherosclerotic plaque formation. Platelet adhesion to plaque-prone sites of arteries, which requires vascular endothelial cell

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**Table 2**

Clinical laboratory data in CAD patients treated with statins.

| Parameter         | All patients \((n=91)\)          |
|-------------------|---------------------------------|
| LDL-C, mg/dL      | \(86\pm26\)                     |
| HDL-C, mg/dL      | \(47\pm12\)                     |
| TG, mg/dL         | \(138\pm73\)                    |
| FBS, mg/dL        | \(108\pm34\)                    |
| HbA1c, %          | \(7.0\pm1.3\)                   |
| eGFR, ml/min/1.73 m\(^2\) | \(58.2\pm19.2\)            |
| UA, mg/dL         | \(5.6\pm1.8\)                   |
| hs-CRP, mg/dL     | \(0.08\) (0.03 to 0.40)        |
| VWF, IU/mL        | \(0.78\pm0.71\)                 |
| Mean              | \(0.78\pm0.71\)                 |
| Median            | \(0.51\) (0.27 to 1.09)        |
| SBP, mm Hg        | \(128\pm18\)                    |
| DBP, mm Hg        | \(70\pm12\)                     |

Data are presented as mean \(\pm SD\) or median (interquartile range).

CAD = coronary artery disease, DBP = diastolic blood pressure, eGFR = estimate glomerular filtration rate, FBS = fasting blood sugar, HbA1c = hemoglobin A\(_1c\), HDL-C = high-density lipoprotein cholesterol, hs-CRP = high-sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TG = triglyceride, UA = uric acid, VWF = von Willebrand factor.

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**Table 3**

Gray-scale IVUS and IB IVUS parameters.

| Parameter                  | All patients \((n=91)\)          |
|----------------------------|---------------------------------|
| Lesion length, mm          | \(15.7\pm7.7\)                  |
| 2D IVUS parameters at the most diseased cross-section |                           |
| Gray-scale IVUS            |                                  |
| Plaque area, mm\(^2\)      | \(9.7\pm4.4\)                   |
| Vessel area, mm\(^2\)      | \(11.6\pm4.5\)                  |
| Lumen area, mm\(^2\)       | \(1.9\pm0.5\)                   |
| Percent plaque area, %     | \(81\pm7\)                      |
| Remodeling index           | \(0.96\pm0.19\)                 |
| IB IVUS                    |                                  |
| Lipid area, %              | \(57\pm16\)                     |
| Fibrosis area, %           | \(36\pm15\)                     |
| Dense fibrosis area, %     | \(5\pm3\)                       |
| Calcification area, %      | \(2\pm2\)                       |
| 3D IVUS parameters         |                                  |
| Gray-scale IVUS            |                                  |
| Total atheroma volume, mm\(^3\) | \(85\pm37\)                  |
| Vessel volume, mm\(^3\)    | \(122\pm44\)                    |
| Percent atheroma volume, % | \(68\pm12\)                     |
| IB IVUS                    |                                  |
| Lipid volume, %            | \(56\pm16\)                     |
| Fibrosis volume, %         | \(36\pm11\)                     |
| Dense fibrosis volume, %   | \(6\pm4\)                       |
| Calcification volume, %    | \(2\pm2\)                       |

Data are presented as mean \(\pm SD\).

2D = two-dimensional, 3D = three-dimensional, IB = integrated backscatter, IVUS = intravascular ultrasound.

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**Figure 2**

Associations between VWF levels and IVUS parameters. PAV (A), lipid volume (B), fibrosis volume (C), dense fibrosis volume (D), and calcification volume (E). IVUS = intravascular ultrasound, PAV = percent atheroma volume, VWF = von Willebrand factor.
reported that blockade of NO production increased VWF levels was found in our study. Elevated VWF levels may reflect impaired endothelial NO production and improves vascular cardiovascular diseases.

Furthermore, a strong association between the extent of atherosclerosis in both the aortic arch and the carotid arteries and VWF levels in patients with transient ischemic attack or ischemic stroke has been reported. A recent study using IVUS also showed that higher VWF levels were associated with a higher coronary plaque burden in CAD patients. Similarly, a positive association between the VWF level and coronary plaque burden was found in our study. Elevated VWF levels may reflect impaired endothelial NO generation in vascular endothelial dysfunction and advanced atherosclerosis in patients with atherosclerotic cardiovascular diseases.

Table 4

| Univariate factors associated with PAV. | r  | P value |
|----------------------------------------|----|---------|
| Age                                    | 0.04 | .77     |
| Male gender                            | 0.01 | .92     |
| BMI                                     | 0.05 | .70     |
| Hypertension                           | 0.03 | .82     |
| Diabetes mellitus                      | 0.19 | .11     |
| Current smoking                        | 0.06 | .64     |
| LDL-C                                  | 0.08 | .08     |
| HLD-C                                  | 0.07 | .57     |
| TG                                     | 0.08 | .53     |
| eGFR                                   | 0.11 | .39     |
| UA                                     | -0.07 | .58     |
| hs-CRP                                 | 0.08 | .52     |
| VWF                                    | 0.39 | .001    |

Table 5

| Multivariate factors associated with PAV. | β  | SE  | F value | P value |
|------------------------------------------|----|-----|---------|---------|
| 1. VWF                                   | 0.26 | 1.72 | 7.44    | .01     |
| 2. Diabetes mellitus                     | 0.17 | 2.78 | 2.99    | .09     |

activation but not actual endothelial denudation, is the initial step in plaque formation. This process is inhibited by the inactivation of VWF in a rabbit model. In addition, the formation of fatty streaks in VWF-deficient mice is delayed compared with that in control mice. VWF and/or the state of endothelial activation reflected by increased VWF levels may contribute to the pathogenesis of early atherosclerotic plaques.

Endothelial dysfunction, which is characterized by impaired bioavailability of endothelial-derived nitric oxide (NO), is involved in the development of atherosclerosis. Endothelial NO plays a crucial role in vasodilation, platelet aggregation, vascular smooth muscle proliferation, and endothelial-leukocyte interactions. Several studies have demonstrated that atherosclerotic arteries decrease NO production. It has been reported that blockade of NO production increased VWF levels in humans. NO may be an inhibitor of endothelial VWF secretion. Several human studies have reported a positive association between VWF levels and the risk of CAD. Furthermore, a strong association between the extent of atherosclerosis in both the aortic arch and the carotid arteries and VWF levels in patients with transient ischemic attack or ischemic stroke has been reported. A recent study using IVUS also showed that higher VWF levels were associated with a higher coronary plaque burden in CAD patients. Similarly, a positive association between the VWF level and coronary plaque burden was found in our study. Elevated VWF levels may reflect impaired endothelial NO generation in vascular endothelial dysfunction and advanced atherosclerosis in patients with atherosclerotic cardiovascular diseases.

Statin is an established treatment for the prevention of cardiovascular events and has several pleiotropic effects. Statin increases endothelial NO production and improves vascular endothelial injury. In addition, statin has a beneficial effect on coagulation and the fibrinolysis cascade. It has been reported that statin therapy reduced VWF levels in ACS patients. Bruni et al reported that statin decreased VWF levels in patients with hypercholesterolemia, and the change in plasminogen activator inhibitor 1 level, which is a marker of endothelial function, was directly related to the reduction in the VWF level. NO may suppress VWF secretion and statins increase endothelial NO generation. Therefore, the effect of statins on the reduction in VWF may be partially attributed to the improvement of endothelial dysfunction after statin therapy. In our study, all of the patients had already received statins, and LDL-C levels were appropriately lowered (86 ± 26 mg/dL) according to the Japanese guidelines. Although VWF levels before the initiation of statin treatment were unclear, the mean VWF level in our study (0.78 ± 0.71 IU/mL) was lower than that of other CAD patients reported in a large-scale study (1.15 ± 2.00 to 1.39 ± 3.01 IU/mL). Since statins produce coronary plaque regression, and may decrease VWF levels, our results may have been influenced by the statin treatment regimen. However, in our study, the LDL-C levels were not associated with either the coronary plaque burden or the VWF levels (data not shown). In addition, the positive association between the VWF levels and the plaque burden was independent of both LDL-C levels and conventional risk factors. These results suggest that high VWF levels may be a marker of the residual cardiovascular risk after statin treatment in CAD patients.

It has been reported that VWF levels are elevated in patients with AF. Also, anticoagulation therapy may influence the VWF level in AF patients. In this study, 9 patients had AF and were receiving OACs (Table 1). However, there was no significant difference in the level of VWF between patients with and without (data not shown). In addition, antiplatelet agents have been reported to affect VWF levels. In this study, all of the patients were already receiving dual antiplatelet therapy (aspirin and thienopyridines) before measurement of the VWF level and the IVUS examination (Table 1). VWF level may be affected by a thrombogenic status including AF and anti thrombotic therapy. Further studies will be needed to clarify these issues.

Since VWF levels are considered to be strongly increased in the acute phase of vascular diseases, ACS patients were not included in this study. It has been reported that there was no significant association between VWF levels and the coronary plaque burden in ACS patients. Increased VWF levels as a result of an acute-phase reaction in ACS may not be useful as a marker of coronary atherosclerosis.

In most previous studies, VWF antigen levels were measured as representative of plasma VWF levels. It is possible that the functional activity of VWF might be more important for investigating the association between VWF and coronary atherosclerosis. However, it is not currently feasible to evaluate VWF functionality.

Recently, different classes of drugs that directly interfere with the VWF pathway, such as monoclonal antibodies, nanobodies, and aptamers, have been developed. These novel drugs have been reported to safely exert powerful antithrombotic effects. To assess the effectiveness of these new drugs on coronary atherosclerosis, large-scale, prospective and randomized clinical trials are required.

The present study has several limitations. First, since the sample size in this single-center study is small, our results should be interpreted carefully. A large-scale multicenter study using
IVUS will be needed to confirm our results. Second, CAD patients who did not undergo IVUS-guided PCI, who had unanalyzable IVUS findings, who were not receiving statins before PCI or whose blood samples could not be corrected for the measurement of VWF levels were not included in this study. In addition, the duration of enrollment in this study was 4 years, which may have been too long for the enrollment of only 91 patients. Therefore, the results may be affected by selective bias and may not be applicable to all CAD patients. Third, we performed IVUS examination only at the PCI site. Ethical considerations precluded the assessment of multiple plaques using IVUS in 3-vascular coronary trees, due to concerns regarding complications of IVUS examination such as coronary spasm and transient ischemia. Fourth, this study did not examine the relationships between the changes in VWF levels and the progression/regression of coronary plaque. A prospective study with serial IVUS examinations will be needed to investigate this issue. Fifth, both the type and dose of statin and the duration of statin treatment before IVUS examination are unknown. At present, it is unclear what type of statin is the best choice or whether a higher dose of statin is useful for more strongly decreasing the VWF level. The type, dose, and duration of other medications such as antihypertensive and antiplatelet agents before enrollment are also unclear. These factors may affect the association between the coronary plaque burden and VWF levels.

5. Conclusions

Higher VWF levels were associated with a higher coronary plaque burden in CAD patients who had been treated with statins, suggesting that a high VWF level may be a marker of the residual cardiovascular risk after statin treatment.

Author contributions

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