Vitronectin concentrations predict risk in patients undergoing coronary stenting

Running Title: GP IIb/IIIa inhibitor and cardiac events

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**Background:** Vitronectin is a multifunctional protein with a multiple binding domain that interacts with a variety of plasma and cell proteins. Vitronectin binds multiple ligands, including the soluble vitronectin receptor (sVNR). Abciximab binds equally well to sVNR and glycoprotein IIb/IIIa, as both share the $\beta_3$ subunit. We tested whether vitronectin concentrations correlate with adverse outcomes in acute coronary syndrome patients.

**Methods and Results:** Baseline serum samples ($n=233$) from a randomized, placebo-controlled trial of abciximab plus stenting (EPISTENT) were retrospectively analyzed. We stratified vitronectin concentrations into the three lower quartiles ($n=178; <49.7 \mu g/ml$) versus the fourth upper quartile ($n=55; \geq 49.7 \mu g/ml$). The endpoint was major adverse cardiovascular event (MACE) defined as death, MI or urgent revascularization at 30 days and 6 months. A higher proportion of patients with baseline vitronectin $\geq 49.7 \mu g/ml$ had MACE than patients with baseline vitronectin $<49.7 \mu g/ml$ at 30 days (18.2% vs. 5.6%; $p=0.01$) and 6 months (20.0% vs. 6.2%; $p=0.006$). When baseline variables not predictive of MACE (e.g., troponin positive, history congestive heart failure, diabetes, history of hypertension, smoking status) were excluded from the multivariate model, only baseline vitronectin $\geq 49.7 \mu g/ml$ (at 30 days: OR 3.23; 95% CI 1.23, 8.49; at 6 months: OR 3.36; 95% CI 1.33, 8.52) and history of myocardial infarction (at 30 days: OR 5.02; 95% CI 1.41, 17.9; at 6 months: OR 3.99; 95% CI 1.28, 12.43) remained. No interaction occurred between abciximab and vitronectin.

**Conclusions:** Our findings indicate that vitronectin may be an independent predictor of adverse cardiovascular outcomes following acute stenting.

**Key words:** vitronectin, stents, glycoproteins
Acute coronary syndromes feature platelet activation and aggregation, thrombus formation, and infarction. C-reactive protein (CRP), sCD40, myeloperoxidase, and decreased concentrations of interleukin-10 are also associated with increased cardiovascular mortality in acute coronary syndrome patients. Treatment with glycoprotein IIb/IIIa (GP IIb/IIIa) antagonists is effective. GP IIb/IIIa and the soluble vitronectin receptor (sVNR) share a common β subunit and are from the same integrin subfamily. Abciximab, a GPIIb/IIIa antagonist approved for use in patients with an acute coronary syndrome or undergoing elective PCI with stenting, also binds to the vitronectin (αvβ3) receptor on platelets and smooth muscle cells. Data indicate that the extra-platelet actions of abciximab may be at least in part responsible for its observed treatment benefit; however, direct associative data are not available.

Vitronectin is present in plasma, the extracellular matrix, and in the granules of blood platelets. It belongs to the group of adhesive glycoproteins that is involved in various functions including complement activation, blood coagulation, binding to proteoglycans, and modification of the matrix. Vitronectin plays a key role in the attachment of cells to their matrix and is involved in the regulation of cell differentiation, proliferation, migration and morphogenesis. Vitronectin and sVNR are present in human atheromatous plaques, suggesting that they may be implicated in atherosclerosis and restenosis. Plasma vitronectin levels were significantly increased in patients with coronary artery diseases, showing a positive correlation with severity of the disease. Using data from a randomized, placebo-controlled trial of abciximab in patients undergoing percutaneous coronary intervention, we tested the hypothesis that patient
serum concentrations of vitronectin and soluble vitronectin receptor correspond to cardiovascular outcomes at 30 days and 6 months following revascularization.
METHODS

This is a retrospective analysis of patient data from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial. The primary trial results have been previously reported. In the primary trial, patients were randomly assigned to placebo with standard-dose heparin or abciximab (Centocor and Eli Lilly, Indianapolis, IN) with low-dose heparin while undergoing coronary stenting. Heparin was administered at a standard dose of 100 U/kg (maximum 10,000 U) or at a low dose of 70 U/kg (maximum 7000 U) with abciximab administered at 0.25 mg/kg up to 60 minutes before intervention, followed by 0.125 μg/kg/min (maximum 10 μg/kg/min) for 12 hours. The primary endpoint was the composite of all-cause mortality, myocardial infarction or re-infarction, or severe myocardial ischemia requiring urgent coronary-artery bypass surgery or revascularization (MACE) through 30 days and 6 months following intervention.

Our sample subgroup population was selected from the first 899 consecutively randomized EPISTENT patients who participated in the Angiographic Substudy, who were the only patients with baseline blood samples stored for the analysis of predictive biomarkers. We took a random sample (n=234) of these 899 patients who had blood samples available for analysis for the determination of vitronectin and sVNR serum concentrations. Among these patients, 233 had vitronectin data available and 231 also had sVNR data available. The protocol for the EPISTENT trial, including the collection of all patient blood samples for biomarker analysis, was approved by the institutional review board or independent ethics committee for each trial site. All patients provided written informed consent.
Baseline patient sera were collected before study treatment and were stored at the EPISTENT trial central laboratory. For this study, these samples were obtained and measured by ELISA (CellTrend, Luckenwalde, Germany) for serum concentrations of vitronectin and sVNR. Serum samples were diluted and then measured in the linear range of the ELISAs. The limit of detection was 10 ng/ml for vitronectin and 7 ng/ml for sVNR, and the intra-assay variation was 3.6% and 4.2%, respectively. The ELISA for vitronectin uses clones VN58-1 (#M017) and VN49-1 (#M016), which are both directed against the N-terminal region of vitronectin (aminoacids 1-130), and recognizes both free and bound vitronectin. The recovery rate of free vitronectin added to serum is between 89% and 118%, suggesting that the epitope of the antibodies used in the ELISA is not masked by the binding sites for other molecules. The ELISA for sVNR is a competitive ELISA. The first antibody is directed against the β3 subunit, the second one against the αv subunit of the receptor. Cross-reactivity to related integrin receptors was excluded. All analyses were performed at the research laboratory of the Charité, Campus-Buch (Berlin, Germany) under blinded conditions.

**Statistical Analysis**

To distinguish between patients with different degrees of cardiac risk, we used an exploratory approach. No formal multivariate testing was performed. We performed logistic regression analysis for dichotomous variables. Wald confidence intervals (95%) for odds ratios were constructed where appropriate. For time-to-event data, survival curves were estimated using the Kaplan-Meier product-limit method. The log-rank test
was used for treatment comparisons. S-Plus 6.1 Professional or the SAS System 8.02 was
used for all analyses.

The authors had full access to the data and take responsibility for its integrity. All
authors have read and agree to the manuscript as written.
RESULTS

At baseline, serum concentrations of vitronectin and sVNR were not associated with hypertension, diabetes, serum troponin concentration, or unstable angina; the only statistically significant difference observed was that patients aged <60 years had higher baseline vitronectin concentrations than patients aged 70-79 years (p<0.001; Table 1). The median serum concentration was 38.2 μg/ml (range 7.5-101.8 μg/ml) for vitronectin and 1.4 μg/ml (range 0.4-25.2 μg/ml) for sVNR (Table 2). At 30 days, MACE rates in the placebo plus stent and abciximab plus stent groups for this subpopulation (11.3% vs. 5.5%, p=0.159) were similar to those for the overall EPISTENT population (10.8% vs. 5.3%, p<0.001). The observed early divergence suggests that the differential patient outcomes were related to increased MACE shortly following intervention.

To test for possible association between vitronectin and MACE and between sVNR and MACE, we first explored baseline serum concentrations of vitronectin and sVNR as continuous variables. The results from this analysis were similar and not significant. Cutpoints at the median and the third quartile were also explored. Baseline sVNR serum concentrations were not associated with 6-month MACE in patients for the median (<1.35 μg/ml vs. ≥1.35 μg/ml; 8.0% vs. 11.0%) or third quartile cutpoints (<2.21 μg/ml vs. ≥2.21 μg/ml; 9.4% vs. 9.8%), and were excluded from further analysis. While baseline serum concentrations of vitronectin were associated with 6-month MACE with both cutpoints, we chose to use the cutpoint at the third quartile for vitronectin (<49.7 μg/ml vs. ≥49.7 μg/ml) because it provided the better dichotomous boundary of the cutpoints we explored (Figure 1). Subsequent analyses of this patient subpopulation were stratified using this cutpoint for baseline vitronectin serum concentration. Baseline

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characteristics were generally similar across this cutpoint, and no differences between
patients with < versus ≥ 49.7 μg/ml baseline serum vitronectin were statistically
significant (Table 2).

Univariate analysis demonstrated that patients with baseline vitronectin ≥49.7
μg/ml were significantly more likely than patients with baseline vitronectin <49.7 μg/ml
to experience MACE at 30 days (18.2% vs. 5.6%; p=0.01) and 6 months (20.0% vs.
6.2%; p=0.006). A multivariate logistic regression model demonstrated that vitronectin
≥49.7 μg/ml was significantly associated with an increased risk of MACE at 30 days (OR
3.94; 95% CI 1.37, 11.33; p=0.011) while treatment with abciximab tended to reduce
MACE (OR 0.37; 95% CI 0.11, 1.23; p=0.105) (Figure 2A). Other variables such as
baseline troponin, history of congestive heart failure and diabetes were not significant
predictors of MACE. When these were excluded from the model, only baseline
vitronectin ≥49.7 μg/ml (OR 3.23; 95% CI 1.33, 8.52; p=0.0104) and history of myocardial
infarction remained (OR 5.02; 95% CI 1.41, 17.9) (Figure 2B). Baseline vitronectin
≥49.7 μg/ml (OR 3.36; 95% CI 1.33, 8.52; p=0.0104) and history of myocardial
infarction (OR 3.99; 95% CI 1.28, 12.43; p=0.0172) were similarly predictive of the risk
of MACE through 6 months (data not shown).

The Kaplan-Meier estimates of the 6-month MACE rates following intervention
are shown in Figure 3, stratified by baseline vitronectin serum concentration and
treatment. The log rank test (p=0.013) revealed a statistically significant difference
between the placebo and abciximab/stent treatment groups stratified by vitronectin (<49.7
μg/ml; ≥49.7 μg/ml). A greater treatment benefit for the MACE rates was observed in the
abciximab/stent group over the placebo group in those subjects with low vitronectin
(<49.7 μg/ml) (Figure 4). Since abciximab directly binds to the vitronectin receptor with high affinity, we investigated if the effects of abciximab on cardiovascular outcomes after PCI were dependent on basal vitronectin levels. Interactions between vitronectin and treatment with abciximab were not significant at the 5% level.
DISCUSSION

The major finding of our study is that vitronectin was an independent risk factor for adverse cardiovascular events in patients with ischemic heart disease undergoing percutaneous interventions with stenting in the EPISTENT trial. Baseline vitronectin serum concentrations were independent from other cardiovascular risk factors, such as hypertension and diabetes mellitus. Furthermore, the presence of an acute coronary syndrome did not influence the observed baseline vitronectin serum concentrations.

We raised this hypothesis because of the pivotal role of the vitronectin/vitronectin receptor system in atherosclerosis and endothelial dysfunction. The therapeutic activity of GPIIb/IIIa antagonists depends on the ability to block platelet aggregation. Abciximab binds to GPIIb/IIIa and to the integrin receptor αvβ3 “vitronectin” receptor (CD51/CD61) with equal affinity, and also binds to the Mb2 “Mac-1” receptor (CD11b/CD18). Since abciximab can target the vitronectin receptor, we reasoned that its efficacy could be related in part to this target.

Vitronectin can be expressed and generated in the vessel wall, particularly in atherosclerotic lesions. Several studies have found a regulatory function for vitronectin in the hemostatic response to vascular injury. Plasma levels of vitronectin were found to be increased in a small cohort of 62 patients with coronary artery disease (CAD) when compared with controls. Thus vitronectin may serve as a marker for CAD and elevated levels may indicate its role in the genesis and/or progression of CAD.

The vitronectin αvβ3 receptor is widely expressed on endothelial and smooth muscle cells, but also on platelets, macrophages, and neutrophils. Endothelial cells in the microvessels of atherosclerotic plaques exhibit high vitronectin receptor expression.
Besides vitronectin, other ligands such as fibrinogen, thrombospondin, and prothrombin also bind to the vitronectin receptor. The vitronectin receptor has important physiological functions including bone resorption, tumor invasion, metastasis, cell adhesion, and spreading.

Data from animal studies support the utility of vitronectin receptor blockade in restenosis. Thus, the vitronectin receptor is an attractive candidate for coronary disease interventions. The reactivity of abciximab with the vitronectin receptor raises the possibility that abciximab, or other agents that inhibit the receptor, may be useful in preventing or treating disorders in which these receptors play a role.

In our retrospective analysis, we measured vitronectin and sVNR in the serum of patients enrolled in the EPISTENT trial. We assume that the vitronectin receptor exists in serum in a soluble form as microparticles because of receptor shedding from the surface of platelets, neutrophils, endothelial cells. Minagar and colleagues found sVNR in the circulation of patients with multiple sclerosis, reflecting chronic inflammation. Serebruany et al. studied the effect of soluble platelet biomarkers, including sVNR, as well as receptor platelet expression in 41 randomized patients with myocardial infarction and found that tenecteplase appeared to have an advantage over alteplase in deactivating platelets. The underlying mechanism leading to sVNR detection in the serum has not been understood. Detached endothelial cells as well as microparticles from activated endothelial cell monolayers might be involved in this process. However, we did not find any change in sVNR in our cohort.

Although several studies have shown a prognostic value of biomarkers in patients with chronic stable angina, in general these patients have not been well characterized.
by biomarkers assessing prognosis, selection of therapeutic approaches, or titration of therapeutic agents.\textsuperscript{33-35} Our study found that measuring vitronectin serum concentrations enabled the identification of a group of patients at particularly high risk of MACE after coronary intervention with stenting. This finding suggests that vitronectin could serve as a biomarker of coronary risk following stenting. While we were unable to compare vitronectin with other markers such as C-reactive protein or sCD40 ligand, vitronectin was not associated with troponin T concentrations or risk factors such as hypertension or diabetes. As a new biomarker, especially one that may not be duplicative of established biomarkers, vitronectin could provide important new insights into pathophysiology and aid in the diagnosis and management of cardiovascular patients.\textsuperscript{36}

Whether vitronectin is solely a marker of disease activity or also has direct consequences for our patients remains uncertain. Although the interaction term between treatment and vitronectin was not significant, it is likely that this analysis was underpowered as the trial from which our sample population was selected was not designed to study this possible relationship. As studies aimed for detecting interaction between treatment and event rates should ideally be strongly powered and comprise a large patient sample population, the results of our study should be interpreted with caution given our sample size of only 233 patients and the low MACE rates observed at 30 days (8.6\%) and 6 months (9.4\%). Finally, the observed lower relative percent reduction in MACE in abciximab-treated patients in the high vitronectin subgroup compared to the low vitronectin subgroup could represent an interference with abciximab efficacy, but this would need to be confirmed in much larger, more appropriately powered study. Likewise, the EPISTENT trial was not designed or powered to explore
the relationship between possible baseline markers of disease activity and event rates;
consequently, these respective findings should also be interpreted with caution.

We believe our findings implicate that vitronectin may be clinically relevant as a biomarker for adverse cardiovascular outcomes in patients with ischemic heart disease undergoing coronary intervention. Vitronectin was an independent risk predictor in this substudy of patients in the EPISTENT trial and may be a potential drug target for agents directed against GPIIb/IIIa receptors. Moreover, vitronectin could have active consequences for patients with acute coronary syndromes and may provide an additional pathogenic pathway that has yet been investigated. Further studies are warranted to explore these possibilities.
ACKNOWLEDGMENTS

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DISCLOSURES

Drs. Barnathan and Agarwal are employees of Centocor Research and Development, Inc.

Dr. Heidecke is an employee of CellTrend.
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FIGURE LEGENDS

Figure 1. Percentage of patients with major adverse cardiovascular events (MACE) at 6 months, stratified by baseline vitronectin serum concentration at the median (left) or the third quartile (right).

Figure 2. Odds ratio estimates for the logistic regression of 30-day major adverse cardiac events (MACE): (A) multivariate model and (B) with independent predictors only and treatment forced into the model.

Figure 3. Kaplan-Meier estimates of the percent of patients with major adverse cardiac events (MACE) through 6 months, presented by baseline vitronectin serum concentration stratified at the third quartile (left) and by treatment (right).

* Cumulative number of patients who experienced MACE through 180 days in each group.

Figure 4. Percent of patients with major adverse cardiac events (MACE) at 30 days (left) and 6 months (right), presented by treatment and baseline vitronectin serum concentration stratified at the third quartile (49.7 μg/ml).

P-values were calculated using the two-sided Fisher’s exact test.
Table 1. Baseline soluble vitronectin receptor (sVNR) and vitronectin serum concentrations in relation to other baseline patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>sVNR (μg/ml)</th>
<th>Vitronectin (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>With unstable angina within 48 hours of intervention</td>
<td>46</td>
<td>2.05</td>
</tr>
<tr>
<td>Without unstable angina within 48 hours of intervention</td>
<td>184</td>
<td>1.88</td>
</tr>
<tr>
<td>P-value</td>
<td>0.624</td>
<td></td>
</tr>
</tbody>
</table>

Troponin ≥0.1 ng/ml

| Troponin >0.1 ng/ml | 42  | 2.59 | 4.04 | 42  | 40.28 | 17.7 |
| Troponin <0.1 ng/ml | 171 | 1.68 | 1.15 | 173 | 38.42 | 15.7 |
| P-value              | 0.156 |       | 0.503 |   |       |     |

With a history of diabetes

| With a history of diabetes | 47  | 1.92 | 1.58 | 48  | 39.05 | 14.65 |
| Without a history of diabetes | 184 | 1.91 | 2.2  | 185 | 40.24 | 17.01 |
| P-value                    | 0.972 |       | 0.658 |   |       |     |

With a history of hypertension

| With a history of hypertension | 118 | 1.92 | 2.49 | 120 | 39.12 | 16.29 |
| Without a history of hypertension | 113 | 1.9 | 1.58 | 113 | 40.93 | 16.79 |
| P-value                       | 0.942 |       | 0.405 |   |       |     |

Age <60 years

| Age <60 years | 112 | 1.85 | 1.45 | 114 | 42.59 | 16.07 |
| Age 60-69 years | 71  | 2.08 | 2.99 | 71  | 40.72 | 17.84 |
| P-value (<60 vs. 60-69 years) | 0.547 |       | 0.462 |   |       |     |

Age 70-79 years

<p>| Age 70-79 years | 47  | 1.83 | 1.77 | 47  | 32.86 | 13.66 |</p>
<table>
<thead>
<tr>
<th>P-value (&lt;60 vs. 70-79 years)</th>
<th>0.941</th>
<th>&lt;0.00</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td></td>
<td></td>
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</table>
Table 2. Baseline patient demographics and disease characteristics, presented by baseline vitronectin serum concentration.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vitronectin &lt;49.7 μg/ml</th>
<th>Vitronectin ≥49.7 μg/ml</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>178</td>
<td>55</td>
<td>233</td>
</tr>
<tr>
<td>Sex, female</td>
<td>42 (23.6)</td>
<td>14 (25.5)</td>
<td>56 (24.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>60.6 (0.80)</td>
<td>55.7 (1.33)</td>
<td>59.4 (0.7)</td>
</tr>
<tr>
<td>Range</td>
<td>35-85</td>
<td>36-77</td>
<td>35-85</td>
</tr>
<tr>
<td>Vitronectin (μg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>33.1 (10.4)</td>
<td>62.5 (12.2)</td>
<td>40.0 (16.53)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>34.8 (7.5-49.6)</td>
<td>58.4 (49.9-101.8)</td>
<td>38.2 (7.5-101.8)</td>
</tr>
<tr>
<td>sVNR (μg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.9 (2.25)</td>
<td>2.1 (1.43)</td>
<td>1.9 (2.09)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>1.3 (0.4-25.2)</td>
<td>1.7 (0.5-6.4)</td>
<td>1.4 (0.4-25.2)</td>
</tr>
<tr>
<td>Current smoker or quit within the previous year</td>
<td>59/177 (33.3)</td>
<td>26/55 (47.3)</td>
<td>85/232 (36.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>91 (51.1)</td>
<td>29 (52.7)</td>
<td>120 (51.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>36 (20.2)</td>
<td>12 (21.8)</td>
<td>48 (20.6)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>87 (48.9)</td>
<td>36 (65.5)</td>
<td>123 (52.8)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8 (4.5)</td>
<td>1 (1.8)</td>
<td>9 (3.9)</td>
</tr>
<tr>
<td>Troponin ≥0.1 ng/ml</td>
<td>32/170 (18.8)</td>
<td>10/45 (22.2)</td>
<td>42/215 (19.5)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) unless noted otherwise.
Figure 1

![Bar graph showing patients with MACE at below median/above median and lower 3 quartiles/upper quartile with corresponding p-values and sample sizes.]

- Below median/above median:
  - Low vitronectin: 5.4%, n=112
  - High vitronectin: 13.2%, n=121
  - p=0.045

- Lower 3 quartiles/upper quartile:
  - Low vitronectin: 6.2%, n=178
  - High vitronectin: 20.0%, n=55
  - p=0.006

Cardiovascular Interventions

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Figure 3

![Graph showing patients with MACE over days for different treatments]

- Vitronectin <49.7 µg/ml
- Vitronectin ≥49.7 µg/ml
- Placebo/Stent Vitronectin ≥49.7 µg/ml
- Abciximab/Stent Vitronectin ≥49.7 µg/ml
- Placebo/Stent Vitronectin <49.7 µg/ml
- Abciximab/Stent Vitronectin <49.7 µg/ml
Figure 4

![Bar chart showing patients with MACE (Major Adverse Cardiovascular Events) at 30 days and 6 months for different quartiles of vitronectin levels, comparing Placebo/Stent and Abciximab/Stent groups.]

- **30 days:***
  - Vitronectin lower 3 quartiles: 8.6% (Placebo/Stent), 2.4% (Abciximab/Stent) (p=0.10)
  - Vitronectin upper quartile: 19.4% (Placebo/Stent), 16.7% (Abciximab/Stent) (p=1.00)

- **6 months:***
  - Vitronectin lower 3 quartiles: 9.7% (Placebo/Stent), 2.4% (Abciximab/Stent) (p=0.06)
  - Vitronectin upper quartile: 22.6% (Placebo/Stent), 16.7% (Abciximab/Stent) (p=0.74)
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