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Background—A proportion of patients who present with suspected acute coronary syndrome (ACS) are found to have insignificant coronary artery disease (CAD) during coronary angiography, but these patients have not been well characterized.

Methods and Results—Of the 5767 patients with non–ST-segment elevation ACS who were enrolled in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (Eptifibatide) Therapy (PURSUIT) trial and who underwent in-hospital angiography, 88% had significant CAD (any stenosis >50%), 6% had mild CAD (any stenosis >0% to ≤50%), and 6% had no CAD (no stenosis identified). The frequency of death or nonfatal myocardial infarction at 30 days was reduced with eptifibatide treatment in patients with significant CAD (18.3% versus 15.6% for placebo, $P=0.006$) but not in those with mild CAD (6.6% versus 5.4%, $P=0.62$) and with no CAD (3.0% versus 1.2%, $P=0.28$). We identified independent baseline predictors of insignificant CAD (mild or no CAD) and used them to develop a simple predictive nomogram of the probability of insignificant CAD for use at hospital presentation. This nomogram was validated in a separate population of patients with non–ST-segment elevation ACS.

Conclusions—Patients with suspected ACS found to have insignificant CAD have a low risk of adverse outcomes, do not appear to benefit from treatment with eptifibatide, and can be predicted with a simple nomogram drawn from baseline characteristics. Because patients with significant CAD appear to have an enhanced benefit from eptifibatide treatment, the predictive nomogram developed can be used to determine indications for glycoprotein IIb/IIIa blockade. **(*Circulation*. 2000;102:1101-1106.)**

Key Words: coronary disease ■ platelets ■ prognosis ■ angiography ■ ischemia

Acute coronary syndromes (ACS) most commonly begin with atherosclerotic plaque rupture and intracoronary thrombus formation.[1] Whereas occlusive intracoronary thrombi are present in most cases of ST-segment elevation myocardial infarction (MI), the degree of coronary blood flow disruption and the morphology of intracoronary thrombi are more diverse in patients who present with non–ST-segment elevation ACS (unstable angina or non–Q-wave MI).[2] Thus, angiographic findings in non–ST-segment elevation ACS range from complex ulcerated lesions to insignificant coronary disease, which occurs in up to 15% to 20% of patients who undergo angiography.[3,4]

Complex lesion morphology is a powerful predictor of adverse outcome in unstable angina, but the impact of insignificant coronary artery disease (CAD) in unstable angina is not clearly understood.[5–8] In the Thrombolysis in Myocardial Ischemia (TIMI)-IIIA trial, 53 (14%) of 391 patients with unstable angina had no critical coronary lesions during angiography and had a low incidence of in-hospital adverse outcome.[9] However, longer-term outcomes and the efficacy of anti-ischemic therapies have not been well characterized in patients with ACS found to have insignificant CAD.

The recent Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (Eptifibatide)

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Therapy (PURSUIT) trial is the largest trial to date of non–ST-segment elevation ACS, with almost 11 000 patients enrolled.[10] In this trial, eptifibatide significantly reduced the composite incidence of death or nonfatal MI at 30 days. We evaluated patients from the PURSUIT trial who underwent angiography and compared the clinical profiles, treatment responses, and outcomes of those with insignificant versus significant CAD.

Methods

Patient Enrollment

The enrollment criteria for the PURSUIT trial have been reported.[10,11] Patients representing 28 countries were enrolled if they presented <24 hours after ischemic chest pain onset with either ECG signs of ischemia or an elevated creatine kinase (CK)-MB level. Patients with persistent ST-segment elevation, active bleeding, or recent major surgery were excluded from enrollment. The study protocol was approved by the institutional review committee of each participating institution, and all patients gave informed consent before enrollment.

Randomization and Treatment

Patients were randomized in a double-blind fashion to placebo or 1 of 2 doses of eptifibatide.[10] In a protocol-specified analysis of the first 3218 patients enrolled, a safety-monitoring committee determined that the higher eptifibatide dose had an acceptable safety profile; thereafter, the low-dose arm was discontinued. The study drug was to be infused until discharge or for 72 hours, whichever occurred first. Aspirin and intravenous heparin were encouraged, and other medications were not restricted.

Coronary Angiography

Decisions about the use of coronary angiography and revascularization were not restricted and were made by the treating physician. The maximum percent stenoses of all major epicardial coronary arteries and bypass grafts were recorded on the case-report form. The percent stenosis of each coronary lesion was determined by the physician performing angiography. Angiographic characteristics of coronary plaques (including intracoronary thrombus) were not recorded. The angiograms were not reviewed in an angiographic core laboratory, and quantitative coronary angiography was not performed.

Patient Selection

The study group consisted of patients who underwent coronary angiography during the initial hospitalization. We excluded patients who did not undergo angiography during the initial hospitalization, those who did not receive study drug after randomization, and those randomized to low-dose eptifibatide treatment.

Patients were separated into 3 groups based on the severity of CAD identified on the baseline diagnostic angiogram. Patients in the significant-CAD group had at least one stenosis >50% in a major epicardial vessel. Patients in the mild-CAD group had at least one stenosis >0% to ≤50%. Patients in the no-CAD group had no coronary stenosis recorded.

After angiography, 9 patients in the mild-CAD group underwent revascularization (8 underwent angioplasty and 1 underwent bypass surgery), as did 3 patients in the no-CAD group (2 underwent angioplasty and 1 underwent bypass surgery). These 12 patients were excluded from further analyses because of concerns that the angiographic findings were not recorded accurately. After exclusion of these 12 patients, the final cohort for this analysis was composed of 5767 patients, 62% of the 9375 patients randomized to and receiving placebo or high-dose eptifibatide.

End Points

The primary end point of the PURSUIT trial (and of this analysis) was a composite of all-cause mortality or nonfatal MI at 30 days. The criteria for MI have been reported.[10] In brief, all suspected infarctions that occurred within 30 days of randomization were independently reviewed and adjudicated by a clinical-events committee blinded to treatment assignment. At the 6-month follow-up, investigators at enrolling sites also determined whether an MI had occurred.

We also analyzed the following end points: 6-month mortality, nonfatal MI at 30 days (as adjudicated by the clinical-events committee), nonfatal MI at 6 months (as determined by investigators), and a composite of death or nonfatal investigator-determined MI at 6 months. Bleeding complications were classified by the TIMI scale,[12] and significant thrombocytopenia was classified as described.[13]

Statistical Analysis

Baseline characteristics were summarized as frequencies and percentages for categorical factors and as medians (25th and 75th percentiles) for the continuous factors. We calculated Kaplan-Meier event rates for patients with significant, mild, or no CAD for the end points evaluated, overall and by treatment assignment. Log-rank tests were used to compare event rates among the 3 disease groups and the treatment effect of eptifibatide within each group.

We used stepwise logistic-regression techniques to identify baseline variables that were independent predictors of insignificant CAD, defined as mild or no CAD. Data from patients in these 2 groups were pooled for this analysis. Candidate variables included demographic, clinical, and ECG factors; initial cardiac enzyme results; and medications used before randomization. The variable "enrollment MI" was adjudicated by the clinical events committee and was defined as any elevation of CK greater than twice the upper limit of normal or CK-MB above the upper limit of normal within 16 hours of randomization. Multivariable predictors were tested by the Wald χ^2 test and retained when $P<0.05$. Results are presented as odds ratios and 95% CIs. We used the coefficients from the full model (as shown in Table 4) to create a simple predictive nomogram.[14] The sum of the scores for each independent predictor represents the probability that a given patient has insignificant CAD.

A C-index value (area under the receiver-operator characteristic curve) was generated for the regression model to measure the concordance of predictions of insignificant CAD with actual angiographic findings. The regression model created from the PURSUIT population in the present study was validated against patients with non–ST-segment elevation ACS enrolled in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO-IIb) trial.[15] The C-index value was recalculated to determine how well this model could discriminate between patients with and without significant CAD in the separate population of patients from GUSTO-IIb who underwent angiography. Finally, another regression model was generated in the GUSTO-IIb population to evaluate all 16 factors in the original PURSUIT model and to determine whether any factors had a different multivariable relationship with the outcome of insignificant CAD than was found in the PURSUIT population.

Results

Patient Characteristics

As seen in Table 1, of the 5767 patients who underwent angiography during the initial hospitalization, 5071 (88%) had significant CAD, 366 (6%) had mild CAD, and 330 (6%) had no CAD. Patients with significant CAD were older, more often male, and more often had diabetes mellitus, hypercholesterolemia, prior MI, prior angina, prior revascularization procedures, enrollment MI, and ST-segment depression compared with patients with mild or no CAD.

In the group with mild CAD, 1 patient had prior bypass surgery, yet all recorded native coronary stenoses were ≤50%. In the group with no CAD, 4 patients had prior angioplasty, and 1 had prior bypass surgery, yet there were no

TABLE 1. Baseline Characteristics by Degree of CAD

	Significant CAD (n=5071)	Mild CAD (n=366)	No CAD (n=330)	P*
Male sex	70.1	52.2	48.2	<0.001
White	88.4	84.1	74.8	<0.001
Age, y	63 (55, 70)	58 (50, 67)	54 (47, 63)	<0.001
Diabetes	23.9	13.1	10.3	<0.001
Hypertension	55.6	55.2	50.3	0.17
Current smoking	30.1	31.1	30.3	0.92
Hypercholesterolemia	46.5	39.9	30.9	<0.001
Family history of CAD	38.7	39.6	36.3	0.64
Congestive heart failure	8.2	7.4	5.5	0.18
Prior MI	33.8	20.5	5.5	<0.001
Prior angina	83.3	72.7	69.5	<0.001
Prior angioplasty	18.2	15.6	1.2	<0.001
Prior bypass surgery	15.9	0.3	0.3	<0.001
Enrollment infarction	48.1	23.6	19.7	<0.001
ECG changes†				
ST-segment depression	47.1	32.2	28.5	<0.001
ST-segment elevation	15.5	14.8	13.0	0.45
T-wave inversion	50.4	60.9	67.0	<0.001

Data are percentages or median (25th and 75th percentiles).
*Across the 3 groups.
†Not mutually exclusive.

recorded stenoses (0%). No adverse clinical events (death or nonfatal MI) had occurred in these patients by 6 months.

Medical Treatment

Study drug was infused for a median 72 (52 and 72 [for 25th and 75th percentiles, respectively]) hours in patients with significant CAD, 72 (30 and 72) hours in patients with mild CAD, and 70 (24 and 72) hours in patients with no CAD. Aspirin was used during the first admission in ≈95% of patients in all 3 groups. β-Blockers were used in 79% of patients with significant CAD, 69% of patients with mild CAD, and 63% of patients with no CAD. Intravenous heparin was used in 96%, 93%, and 92% of patients, respectively.

Outcomes

As seen in Table 2, adverse ischemic events occurred more often in the group with significant CAD. Patients with mild CAD had a lower adjusted risk of the composite of death or nonfatal MI at 30 days than did patients with significant CAD (hazard ratio 0.45, 95% CI 0.25 to 0.80; $P=0.007$). The group with no CAD also had a lower adjusted risk of this composite end point (hazard ratio 0.20, 95% CI 0.08 to 0.49; $P<0.001$). At 6 months, patients with mild or no CAD continued to have a lower risk of adverse events than did those with significant CAD.

TABLE 2. Outcomes by Severity of CAD

	Significant CAD (n=5071)	Mild CAD (n=366)	No CAD (n=330)
30 Days			
Death	3.3	0.5	0.6
Nonfatal MI (by CEC)	15.3	5.7	1.5
Nonfatal MI (by investigators)	8.0	0.8	0.6
Death or nonfatal MI (by CEC)	17.0	6.0	2.1
Death or nonfatal MI (by investigators)	10.0	1.4	0.9
6 Months			
Death	5.5	0.6	1.2
Nonfatal MI (by investigators)	9.9	1.7	1.2
Death or nonfatal MI (by investigators)	13.4	2.2	2.2

Data are percentages. CEC indicates clinical events committee. All $P<0.001$ across the 3 groups for each outcome analyzed.

Treatment Efficacy

As seen in Table 3, the frequency of the composite end point of death or nonfatal MI at 30 days was reduced from 18.3% to 15.6% in patients with significant CAD treated with eptifibatide (absolute risk reduction 2.7%, relative risk reduction 15%; $P=0.006$). The Kaplan-Meier event curves for the frequency of the composite end point separated early during the study drug infusion in the group with significant CAD; thereafter, fewer events were seen in eptifibatide-treated patients through 30 days (Figure 1). By contrast, no apparent treatment benefit was seen in patients who did not have significant CAD. The frequency of the composite end point was similar among patients treated with placebo and those treated with eptifibatide in the group with mild CAD (6.6% versus 5.4%, $P=0.63$) and the group with no CAD (3.0% versus 1.2%, $P=0.28$).

Safety

In all patients treated with eptifibatide, the incidence of major or minor bleeding was highest in the group with significant CAD compared with the groups with mild CAD and no CAD

TABLE 3. Outcomes at 30 Days by Severity of CAD and Treatment Assignment

	Significant CAD			Mild CAD			No CAD		
	Placebo (n=2548)	Eptifibatide (n=2523)	P	Placebo (n=181)	Eptifibatide (n=185)	P	Placebo (n=169)	Eptifibatide (n=161)	P
Death, %	3.7	2.9	0.11	0.6	0.5	0.99	1.2	0.0	0.16
Nonfatal MI %	16.6	14.1	0.009	6.1	5.4	0.77	1.8	1.2	0.68
Death or nonfatal MI, %	18.3	15.6	0.006	6.6	5.4	0.62	3.0	1.2	0.28

Thirty-day outcomes were adjudicated by the clinical events committee.

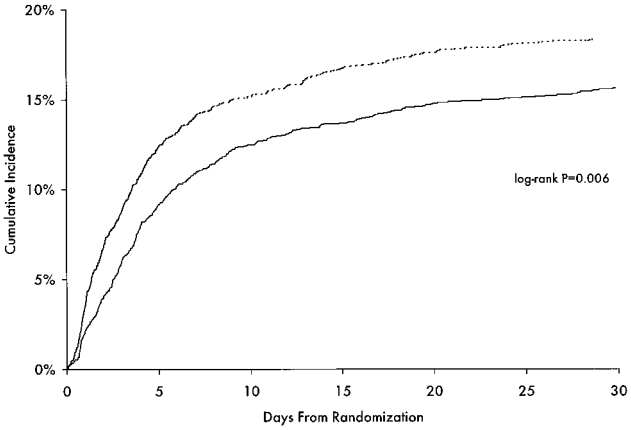

Figure 1. Kaplan-Meier plot of death or nonfatal MI through 30 days in patients with significant CAD receiving eptifibatide (solid line) or placebo (dashed line).

(34.5% versus 9.7% versus 8.1%, respectively; $P<0.001$). Most bleeding events in patients with significant CAD treated with eptifibatide, however, were related to revascularization procedures. The incidence of major or minor bleeding with eptifibatide treatment in patients with significant CAD was 25.8% for patients who underwent angioplasty, 81.7% for those who had bypass surgery, and 13.0% for patients who did not undergo revascularization. Additionally, thrombocytopenia was more common in the group with significant CAD compared with the other groups (10.4% versus 1.2% versus 0.7%, respectively; $P<0.001$).

Predictors of Insignificant CAD

As seen in Table 4, several baseline characteristics were found to predict insignificant CAD (mild or no disease) versus significant CAD. The strongest independent predictors of insignificant CAD included younger age, female sex, and the absence of enrollment MI, prior angina, diabetes, or ST-segment depression. The overall model χ^2 was 947 ($P<0.001$), and the C-index value was 0.827, indicating that the model can reliably predict the presence of insignificant CAD. An estimate of the probability of insignificant CAD can be calculated for individual patients by using the nomogram created from this model (Figure 2).

TABLE 4. Independent Baseline Predictors of Insignificant CAD

	Wald χ^2	P	Odds Ratio (95% CI)
No enrollment MI	178.2	<0.001	4.24 (3.43–5.24)
Age (per 10-y decrease)	143.6	<0.001	1.72 (1.57–1.88)
Female sex	94.7	<0.001	2.51 (2.09–3.03)
No angina <6 wk before entry	63.5	<0.001	2.39 (1.93–2.96)
No diabetes	39.6	<0.001	2.36 (1.81–3.08)
No ST-segment depression	37.7	<0.001	1.82 (1.51–2.21)
No current smoking	29.2	<0.001	1.77 (1.44–2.17)
No previous MI	25.6	<0.001	1.97 (1.51–2.55)
No previous bypass surgery	25.2	<0.001	35.86 (8.86–145.1)
No hyperlipidemia	12.9	<0.001	1.40 (1.17–1.69)
Nonwhite race	11.4	<0.001	1.50 (1.19–1.90)
No peripheral vascular disease	7.4	0.007	2.16 (1.24–3.76)
No β-blocker treatment before entry	6.9	0.009	1.28 (1.07–1.54)
No previous angioplasty	6.3	0.012	1.49 (1.09–2.03)
No ST-segment elevation	4.6	0.032	1.32 (1.03–1.71)
Congestive heart failure	4.3	0.039	1.48 (1.02–2.14)

Model χ^2 value was 947.025; C-index value, 0.827. Of the 5767 patients included in the model, 696 had insignificant CAD.

Figure 2. Nomogram to predict probability of insignificant CAD from baseline clinical characteristics. In panel 1, find values that most closely match patient's baseline characteristics and determine corresponding point assignment. In panel 2, add points for all predictive factors. In panel 3, determine probability of insignificant CAD based on total points.

When the predictive model was applied to the GUSTO-IIb population, the C-index value was 0.796. The validation plot of actual incidence versus predicted probability of insignificant CAD in the GUSTO-IIb population illustrates the excellent discrimination of this model when applied to a different

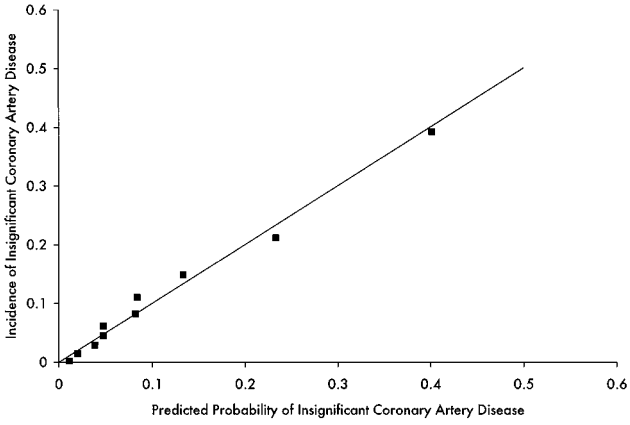

Figure 3. Validation plot for actual incidence vs predicted probability of insignificant CAD in GUSTO-IIb population by deciles of probability. Plot shows excellent concordance of PURSUIT model for insignificant CAD in a separate patient population.

population (Figure 3). Most of the 16 factors in the model derived from the PURSUIT population remained significant when the model was applied to the GUSTO-IIb population. Neither congestive heart failure nor the absence of previous angioplasty was a predictor of insignificant CAD in the GUSTO-IIb population, but these 2 factors were among the least powerful predictors of insignificant CAD in the PURSUIT population (Table 4).

Discussion

Even in this clinical trial that used objective evidence of ischemia as enrollment criteria (chest pain, ECG changes, and cardiac enzyme elevations), a sizable proportion of patients with non–ST-segment elevation ACS were found to have insignificant CAD during coronary angiography. Patients with insignificant CAD had a low incidence of adverse outcomes and did not benefit from treatment with the glycoprotein (GP) IIb/IIIa inhibitor eptifibatide. By contrast, an enhanced treatment effect was demonstrated in patients with significant CAD treated with eptifibatide. Baseline clinical characteristics were used to create a simple model that accurately predicted the probability of insignificant CAD in a separate population of patients.

Although patients with ACS and insignificant CAD have been shown to have better in-hospital outcomes than those experienced by ACS patients with significant CAD, longer-term outcomes have not been closely examined.[9] Our results show a low incidence of death or nonfatal MI through 6 months in patients with insignificant CAD. In previous angiographic studies, however, the progression of coronary lesions in unstable angina has been common and associated with an increased incidence of ischemic events.[16,17] In this analysis, we could not evaluate the angiographic progression of disease, but patients with insignificant CAD had a low risk of adverse clinical events through 6 months. Further evaluation is needed to determine whether patients with insignificant CAD have a similar prognosis through longer-term follow-up.

The underlying mechanisms that contribute to the clinical presentation of ACS in patients with insignificant CAD are not well understood. Because almost 25% of the patients with insignificant CAD in this analysis presented with MI at enrollment, intracoronary thrombus may have first formed at the site of a minimal coronary lesion, as described by Pecora et al.[18] Embolization of platelet-fibrin thrombi to the microvascular circulation, endothelial dysfunction caused by abnormalities in distal coronary flow, or both may also be present in patients with ACS who have no significant coronary epicardial lesions.[9,19,20] Elevated troponin levels are a possible marker of lesion complexity, thrombus burden, and microvascular obstruction in patients with non–ST-segment elevation ACS.[10,21] However, troponin levels were not routinely measured in the PURSUIT trial, so we could not assess their predictive and prognostic abilities in patients with insignificant CAD. Finally, given the limited prognostic significance of T-wave changes in patients with unstable angina, the high prevalence of T-wave inversion in patients with insignificant CAD suggests that these ECG findings may have contributed to the incorrect diagnosis of ACS in a certain proportion of patients.[22]

Because we have demonstrated that patients with insignificant CAD do not benefit from treatment with GP IIb/IIIa blockade, early identification of patients with suspected ACS who have insignificant CAD may help to guide therapeutic decisions in this low-risk cohort. The probability of insignificant CAD can be reliably predicted before angiography by use of baseline characteristics, so the nomogram we created can potentially be used to identify patients who are not likely to benefit from treatment with a GP IIb/IIIa inhibitor on hospital presentation. The clinical significance of our predictive nomogram was demonstrated by the finding that patients with significant CAD treated with eptifibatide had a greater reduction in the frequency of the primary composite end point than did the overall PURSUIT population (2.7% versus 1.5%).[10]

Serum cardiac markers are a simple, reliable diagnostic technique that can be used for the risk stratification of patients presenting with suspected ACS, and they appear to enhance the predictive capabilities of our nomogram. The variable “no enrollment MI” was the strongest predictor of insignificant CAD in our analysis but included events through 16 hours after randomization. Many patients with suspected ACS initially present with normal cardiac-marker levels, which may not become elevated until after hospital admission. However, the nomogram that we have developed is flexible and can be used any time a physician is considering whether to start a GP IIb/IIIa inhibitor. Elevated troponin levels appear to identify patients with ACS who have enhanced benefit from treatment with GP IIb/IIIa blockade, but troponin levels were not measured in the PURSUIT trial and thus could not be incorporated into the predictive nomogram.[23,24] Further study is needed to determine which combination of high-risk features (elevated CK-MB and troponins and ischemic ST-segment changes) can be used together with our predictive nomogram to select patients with suspected ACS who have enhanced benefit from treatment with a GP IIb/IIIa inhibitor.

Limitations

Only patients who underwent angiography were evaluated, so a selection bias relating to the decision to perform angiography may have influenced the results. The angiographic information recorded was limited and did not include assessments of lesion characteristics, intracoronary thrombus, or coronary flow. Additionally, there was no verification of the severity of coronary lesions in an angiographic core laboratory. The PURSUIT trial, however, was designed as a large “simple” trial that enrolled almost 11 000 patients with non–ST-segment elevation ACS.[25] Detailed angiographic analysis and verification of the findings in a core laboratory would have been impractical in a trial of this size. Finally, the enrollment criteria of PURSUIT were designed to select a moderate- to high-risk group of patients with non–ST-segment elevation ACS, so the patient population studied in this analysis may have been “enriched” compared with that seen in typical clinical practice.

Conclusions

Patients with ACS found to have insignificant CAD during coronary angiography have a low risk of adverse outcomes. Whereas patients with insignificant CAD did not appear to benefit from treatment with eptifibatide, those with significant CAD were shown to have an enhanced treatment benefit. Baseline clinical characteristics were used to accurately predict the probability of insignificant CAD by use of a simplified nomogram. Therefore, early identification of patients with suspected ACS who have insignificant CAD may help to refine triage algorithms for acute ischemic chest pain and to determine indications for GP IIb/IIIa inhibitors.

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