original article

Intracoronary epinephrine versus adenosine in the management of refractory no-reflow phenomenon: a single-center retrospective cohort study

Ahmed Darwish, Abdel-Fattah Frere, Magdy Abdelsamie, Waleed El Awady, Mohammad Gouda

From the Department of Cardiology, Zagazig University, Zagazig, Egypt

Correspondence: Dr. Ahmed Darwish · Department of Cardiology, Zagazig University, Zagazig 44519, Egypt · ahmeddarwish9@gmail.com · ORCID: https://orcid.org/0000-0001-8400-3492

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BACKGROUND: The no-reflow phenomenon is associated with a considerable reduction in myocardial salvage in patients with ST elevation myocardial infarction (STEMI) treated by primary percutaneous intervention (PCI). There has been no head-to-head comparison of intracoronary epinephrine to adenosine in the management of no-reflow phenomenon.

OBJECTIVES: Evaluate the short- and long-term efficacy and safety of using intracoronary epinephrine versus adenosine for management of the catastrophic no-reflow phenomenon that may occur during primary PCI.

DESIGN: Retrospective cohort.

SETTING: Single center in Egypt.

PATIENTS AND METHODS: The study included STEMI patients who developed refractory no-reflow phenomenon during primary PCI after failure of conventional treatments and received either intracoronary epinephrine or adenosine.

MAIN OUTCOME MEASURES: No-reflow management measured through improvement of thrombolysis in myocardial infarction grade (TIMI flow), myocardial blush grade, TIMI frame count and major adverse cardiovascular events (MACE) at 1-year follow up.

SAMPLE SIZE: 156 patients with refractory no-reflow phenomenon during primary PCI.

RESULTS: Successful reperfusion was achieved in 74 of 81 (91.4%) of patients who received epinephrine and in 65 of 75 (86.7%) who received adenosine ($P<.05$). Fifty-six of 81 patients (69.1%) achieved TIMI III flow after epinephrine administration versus 39 of 75 patients (52.7%) in the adenosine group ($P=.04$). The incidence of heart failure after 1 year of follow up was lower in the epinephrine group compared to the adenosine group (6.3% vs. 19.2 %, $P<.017$). MACE after 1 year of follow up was lower in patients who received epinephrine compared to those who received adenosine (11.3 % Vs. 26.7 %, $P<.01$).

CONCLUSION: During primary PCI, intracoronary epinephrine is as effective as adenosine in successful management of refractory no-reflow phenomenon with a more favorable long-term prognosis compared to adenosine.

LIMITATIONS: Retrospective design.

CONFLICT OF INTEREST: None.

Primary percutaneous coronary intervention (PCI) is the standard treatment for patients with ST-segment elevation myocardial infarction (STEMI) according to the latest European Society Of Cardiology guidelines.[1] No-reflow, which is not uncommon during primary PCI, is defined as impaired myocardial perfusion that is attributed to microvascular obstruction despite opening the occluded epicardial coronary artery.[2] The frequency of no-reflow phenomenon is reported to be around 0.6–5% in elective cases, but it may be encountered in up to 50% of primary PCI cases.[3] After primary PCI, the presence of the no-reflow phenomenon has a poor prognosis due to a significant reduction in the myocardial perfusion and larger myocardial necrosis that usually impairs left ventricular function and increases cardiovascular mortality.[4] Pharmacotherapy for the management of no-reflow has always taken two main strategies: local vasodilator and antiplatelet therapy. Intracoronary adenosine has been approved by American guidelines in the management of the no-reflow phenomenon.[5] On the other hand, although epinephrine is one of the main agents in resuscitating arrested patients, there is little published data on its effectiveness in coronary no-reflow.[6] This study aimed to evaluate the short- and long-term efficacy and safety of using intracoronary epinephrine versus adenosine for management of the catastrophic no-reflow phenomenon that may occur during primary PCI.

PATIENTS AND METHODS

This single center, retrospective cohort study, was conducted in the catheterization lab in the cardiology department of Zagazig University Hospital, Zagazig, Egypt, from April 2019 to April 2021. Written consent was obtained from patients to review their medical records after explanation of the medical research and publication process. The study was conducted according to the guidelines of the declaration of Helsinki, and approved by the institutional review board of Zagazig University Hospital, Sharkia, Egypt (approval number: ZU-IRB #5316/24-3-2019).

The study included STEMI patients who developed refractory no-reflow during primary PCI. No-reflow was defined as a reduction in antegrade TIMI (thrombolysis in myocardial infarction) flow grade (TIMI 0 and TIMI 1) after stent deployment after ruling out spasm, dissection, and acute stent thrombosis. No-reflow was defined as refractory when it did not resolve with administration of any two of the following medications: nitrates, verapamil and glycoprotein IIb/IIIa inhibitors.[7] We excluded patients with cardiogenic shock at time of admission, known allergy to epinephrine or adenosine, non-ST elevation acute coronary syndrome, patients with electrical instability which contraindicated use of either epinephrine or adenosine such as sinus bradycardia, heart block, junctional rhythm, frequent extrasystoles, non-sustained and sustained ventricular tachycardia (VT), chronic hemodialysis, pregnancy, contraindications to dual antiplatelet therapy, need for emergent coronary artery bypass surgery and patients diagnosed as having COVID-19 using the PCR test (9 patients).

Baseline demographic and clinical data were obtained from all patients and physical examination was done with special attention to evaluate the patients clinically for signs of heart failure depending mainly on the Killip classification.[8] The Grace score also was calculated for risk stratification of all included patients.[9] All patients were premedicated before transfer to the catheterization lab with 300 mg aspirin, 180 mg ticagrelor, 80 mg atorvastatin and unfractionated heparin (70–100 IU/ kg IV bolus when glycoprotein IIb/ IIIa inhibitor was not planned to be used and 50–70 IU/kg when GP IIb/ IIIa inhibitor was planned). The epinephrine regimen consisted of one ampule (1 mg/1 mL) diluted in 10 cc saline then 1 cc of epinephrine diluted 10 fold by adding 1 cc to 10 cc saline for a dose of 100 µg for intracoronary injection over 5 minutes through an aspiration catheter or a pierced balloon inflated at the culprit lesion. This dose could be repeated up to 3 times if needed, reaching a maximum dose of 400 µg. The adenosine regimen consisted of one ampule (6 mg/2 mL) diluted in 10 cc saline then 1 cc of adenosine diluted 10 fold by adding 1 cc to 10 cc saline; 1 cc of the solution was then added to another 10 cc saline to reach final concentration of 60 µg for intracoronary injection through an aspiration catheter or a pierced balloon inflated at the culprit lesion. Another dose was repeated once if needed, reaching a maximum dose of 120 µg.

Calculation of TIMI flow grade, myocardial blush grade (MBG) and TIMI frame count was done before and after drug administration. Procedural success was defined as ≤20% stenosis and improvement of TIMI flow and MBG to grade 2 or 3.[10] Immediately after the procedure, bedside screening echocardiography was done to assess regional wall motion abnormalities, end systolic volume, end diastolic volume, ejection fraction using the Simpson biplane method, pulmonary artery pressure, presence, and degree of mitral regurgitation and other complications of myocardial infarction. We recorded development of acute renal failure and in hospital major adverse cardiac events (MACE) including heart failure, stroke and death. Follow up was done by reviewing patient medical records. In our center, patients are routinely scheduled for follow-up visits weekly

for the first month after discharge then an outpatient visit every three months. Echocardiography assessment is done routinely three months post-primary PCI, one year after the procedure and in cases having any new event.

At the one year follow-up visit, all patients were assessed for regional wall motion abnormalities, left ventricular systolic function, and MACE including heart failure, stroke, recurrent myocardial infarction, repeat revascularization, and death. Heart failure was defined as a new onset of symptoms and/or signs of heart failure plus echocardiographic evidence of systolic dysfunction with ejection fraction less than 40%.

Data were analyzed using IBM SPSS version 23.0 (Armonk, New York, United States: IBM Corp). Qualitative data are shown as number and percentage and quantitative data are shown as mean and standard deviation, or median and interquartile range. The epinephrine and adenosine groups were compared using the independent sample t-test or the Mann-Whitney U test as appropriate. The paired t-test was used to compare the angiographic and echocardiographic parameters before and after drug use in each group separately. A *P* value of <.05 was considered statistically significant.

RESULTS

Of 1356 consecutive patients who presented to our catheterization lab with STEMI and underwent primary PCI from April 2019 to April 2021, 172 (12.7%) patients developed the refractory no-reflow phenomenon. After excluding 16 patients, 156 patients with refractory no-reflow who received either intracoronary epinephrine or adenosine were included in the analysis (**Figure 1**). Eighty-one received epinephrine and 75 received adenosine. The epinephrine group were given a cumulative dose 100-400 µg of intracoronary epinephrine; the adenosine group were given 60-120 µg of intracoronary adenosine over 5 minutes through aspiration catheter or pierced balloon inflated at the culprit lesion. With the exception of age, there was no significant difference between the two groups in demographics and risk factors including hypertension, diabetes, dyslipidemia, and smoking (**Table 1**). For time from symptom onset to primary PCI, there was no statistically significant difference between the two groups (**Table 2**). Successful reperfusion was achieved in 91.4% (75/81) of patients who received epinephrine and 86.7% (65/75) in those who received adenosine for no-reflow management (*P*=.35). The number of patients who achieved TIMI III flow after drug administration was higher in the epinephrine group (**Table 2, Figure 2**). MBG as well was higher in the epinephrine group compared to adenosine group (*P*=.04).

Most of the arrhythmic events in the epinephrine group were sinus tachycardia, which was reported in 28.4% of cases (**Table 3**). However, supraventricular tachycardia and non-sustained VT occurred only in 3.7% and 6.2% of cases in the epinephrine group, respectively, and was spontaneously terminated. Sustained VT was encountered only in one case which was successfully managed by direct current cardioversion. Also, transient heart block occurred in 1.3% of patients who received adenosine. Regarding in-hospital cardiovascular events, heart failure was numerically lower but statistically non-significant in the epinephrine group compared to adenosine. Otherwise, no significant difference was noted in clinical outcomes in the hospital.

At 1-year follow-up, LV ejection fraction showed a statistically significant improvement compared to baseline (56.3 [8.7] vs. 48.9 [7.9]; *P*<.001) in the epinephrine group, and in the adenosine group (54.1 [11.5] vs 49.1 [7.8]; *P*<.001). The difference in ejection fraction between the groups at 1 year was not statistically significant (*P*=.0179). On the other hand, at the 1-year follow up, the incidence of HF among patients who received epinephrine was lower compared to those who received adenosine (6.3% vs. 19.2%, *P*<.017) (**Figure 3**). Overall, MACE at 1 year were lower in the epineph-

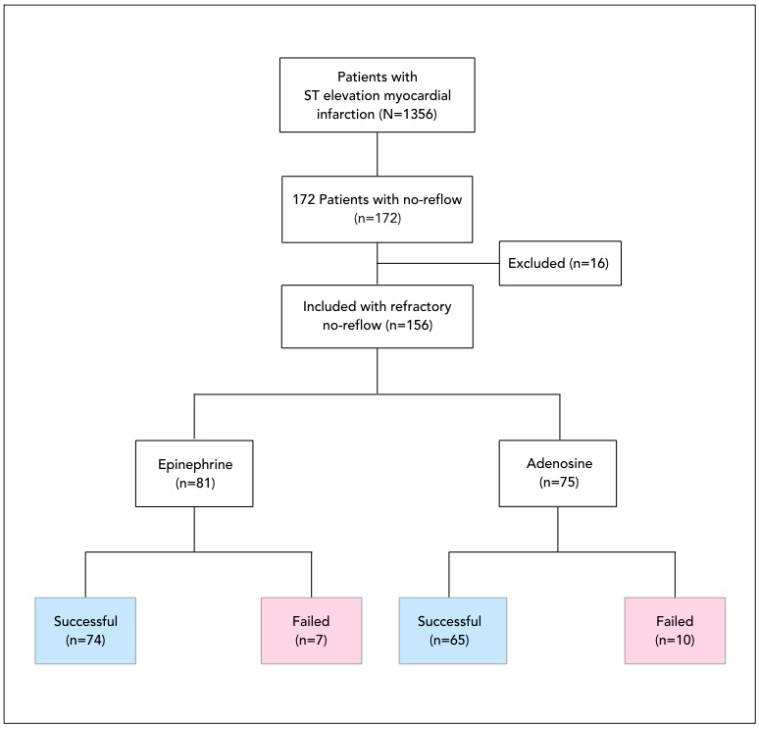

Figure 1. Flow diagram.

Table 1. Demographic data and risk factors for the two groups (n=156).

	Epinephrine (n= 81)	Adenosine (n= 75)	*P* value
Age (median and IQR)	62 (9)	54 (11)	<.001[a]
Gender			
Female	37 (54.3)	29 (38.7)	.376
Male	44 (45.7)	46 (61.3)	
Hypertension	43 (53.1)	44 (58.7)	.483
Diabetes mellitus	56 (69.1)	49 (65.3)	.613
Smoking	34 (42.0)	42 (56.0)	.080
Dyslipidemia	46 (56.8)	45 (60.0)	.685
Peripheral artery disease	2 (2.5)	5 (6.7)	.206
Family history of premature coronary artery disease	9 (11.1)	12 (15.0)	.371

Data are n (%) unless noted otherwise. [a]Mann-Whitney U test.

Table 2. Angiographic analysis of the two groups.

Angiographic variables	Epinephrine (n=81)	Adenosine (n=75)	*P*
Time to PCI (hours)	10 (15)	10 (20)	.329[a]
Diseased vessels	1.53 (0.7)	1.67 (0.7)	.24
Culprit vessel			
Left anterior descending	48 (59.3)	37 (49.3)	.214
Left circumflex artery	17 (21.0)	14 (18.7)	.717
Right coronary artery	16 (19.8)	24 (32)	.08
Aspiration Use	21 (25.9)	20 (26.7)	.92
Reflow (TIMI grade) before drug	0.27 (0.4)	0.41 (0.4)	.06
TIMI 0 after drug	0 (0)	1 (1.4)	.29
TIMI 1 after drug	7 (8.6)	9 (12.2)	.47
TIMI 2 after drug	18 (22.2)	26 (35.1)	.08
TIMI 3 after drug	56 (69.1)	39 (52.7)	.04
Myocardial blush grade after drug	3 (1)	2 (1)	.04[a]
TIMI frame count before drug use	59.07 (9.4)	58.49 (9.4)	.69
TIMI frame count after drug use	19.62 (6.2)	21.48 (6.8)	.076
Successful reperfusion (TIMI 2, 3)			
Yes	74 (91.4)	65 (86.7)	.35
No	7 (8.6)	10 (13.3)	

Data are n (%) unless noted otherwise. [a]Median (IQR), Mann-Whitney U test. TIMI: Thrombolysis in myocardial infarction.

rine group compared to the adenosine group (11.3% Vs. 26.7%, *P*<.01). This difference was attributed to the significant decrease in heart failure events, while differences in other events were statistically non-significant.

DISCUSSION

The development of the no-reflow phenomenon is indicative of a poor prognosis, and is usually associated with a significant reduction in myocardial salvage in patients with STEMI. In response to reduced myocardial perfusion, larger myocardial necrosis occurs, which subsequently impairs left ventricular function and increases mortality.[11] On short-term follow up, the no-reflow phenomenon has been associated in different studies with prolonged hospitalization compared with patients without no-reflow.[12] In a study conducted on 1140 patients, development of no-reflow during primary PCI was associated with larger infarct size, impaired left ventricular systolic function at 6 months and increased 1-year mortality risk. On long-term follow up, no-reflow was proven to be a strong predictor of 5-year mortality.[13,14]

Classically, management of no-reflow depends on intracoronary vasodilator and antiplatelet drugs to target both vasospastic and thromboembolic mecha-

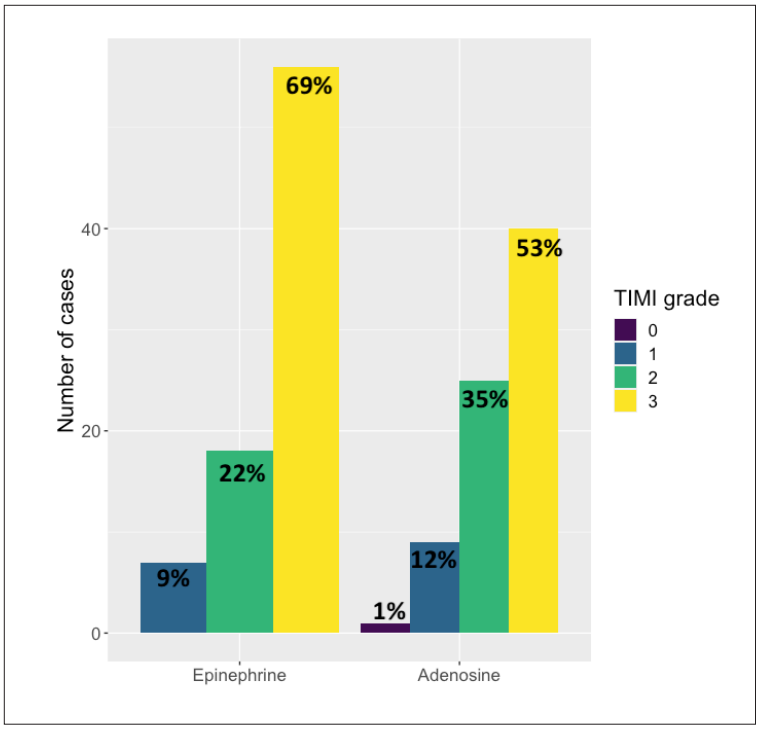

Figure 2. TIMI flow grade after epinephrine and adenosine administration (percent of total for each drug) (see Table 2 for statistical comparisons).

Table 3. Clinical outcomes in hospital and after 1 year.

	Epinephrine (n= 81)	Adenosine (n= 75)	*P* value
In-hospital cardiovascular outcome			
Sinus tachycardia	23 (28.4)	0	<.001
Supraventricular tachycardia	3 (3.7)	0	.09
Non-sustained ventricular tachycardia	5 (6.2)	0	.03
Sustained ventricular tachycardia	1 (1.2)	0	.33
Heart block	0	1 (1.3)	.29
Heart failure	5 (6.2)	8 (10.7)	.310
Death	1 (1.2)	0	.33
Major adverse cardiovascular event	6 (7.4)	8 (10.7)	.477
Acute renal failure	3 (3.7)	1 (1.3)	.35
1-year cardiovascular outcome			
Heart failure	5 (6.3)	14 (19.2)	.02
Recurrent myocardial infarction	2 (2.5)	3 (4.1)	.59
Stroke	1 (1.3)	2 (2.7)	.51
Death	1 (1.2)	2 (2.7)	.52
Major adverse cardiovascular event	9 (11.3)	20 (26.7)	.01

Data are n (%).

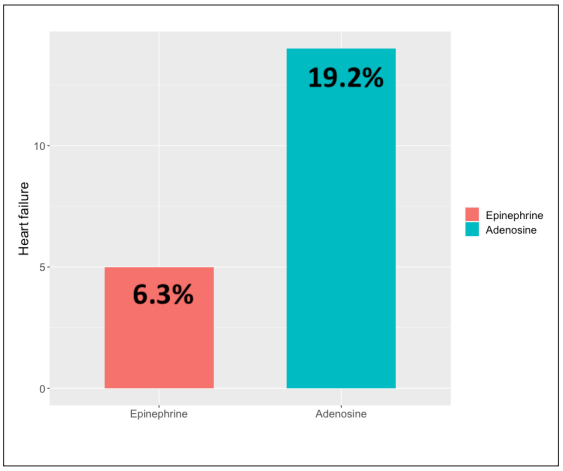

Figure 3. Heart failure events 1 year after epinephrine and adenosine administration (*P*<.017).

nisms, respectively.[5] Despite the availability of pharmacological agents for management of no-reflow, a considerable percentage of cases are still refractory. A recent study has shown that aspiration thrombectomy followed by intracoronary abciximab injection did not improve myocardial reperfusion in STEMI patients undergoing primary PCI.[12] Consequently, the need for a new agent to manage no-reflow, which is a pivotal unsolved issue in the interventional cardiology field, inspired us to conduct this study. The major finding of our study is that both intracoronary epinephrine and adenosine are effective agents in the management of refractory no-reflow phenomenon during primary PCI. In addition, intracoronary epinephrine administration in management of no-reflow phenomenon resulted in fewer 1-year adverse cardiovascular events compared to adenosine. To our knowledge, this is the first head-to-head study that has compared the effect of intracoronary epinephrine to adenosine in the management of no-reflow phenomenon.

The present study demonstrated that intracoronary epinephrine was effective in the management of refractory no-reflow. Such success was observed by significant improvement of both TIMI flow and TIMI frame count after epinephrine administration. This result is in agreement with Skelding et al,[15] Aksu et al[16] and Navarese et al[17] who showed that intracoronary epinephrine administration for management of no-reflow phenomenon during primary PCI yielded significantly better coronary flow patterns compared to those treated with conventional agents alone including nitrates, adenosine, thrombectomy and glycoprotein IIb/IIIa inhibitors. These results may be explained by the well-known inotropic and chronotropic properties of epinephrine.[18] Patients who develop no-reflow usually presented with hypotension; intracoronary epinephrine administration may restore normal blood pressure in those patients by stimulation of alpha vasoconstrictor receptors. In addition, correction of hypotension improves coronary perfusion, which may be another potential mechanism in aborting no-reflow.[19] Another potential explanation for the role of epinephrine in no-reflow is that it has potent beta-2 receptor agonist properties that mediate coronary vasodilatation.[15]

Regarding the safety of epinephrine, sinus tachycardia was the most frequently encountered arrhythmia. Supraventricular tachycardia and VT developed in a minority of patients, which is consistent with the findings of Aksu et al[19] who did not report any sustained VT after intracoronary epinephrine. This lack of sustained VT could be due to distal intracoronary injection of epinephrine rather than its injection through the guide catheter. This explanation is supported by the findings of Abu Arab et al[20] who demonstrated that heart rate changes after guide catheter delivery of medications were greater than changes after local distal delivery through aspiration catheter or pierced balloon.

Adenosine was proven to be effective as well for management of no-reflow phenomenon. This may be explained by the studies showing that regional myocardial blood flow was significantly better in the adenosine-treated animals.[21] The beneficial effect also extended beyond vasodilatation to preservation of vascular endothelium in the ischemic areas.[21]

On the other hand, a major limitation of adenosine is its short half-life. Recent studies revealed that a 2-hour intracoronary adenosine infusion is better than an adenosine bolus in aborting no-reflow. However, the main issue regarding adenosine infusion is that it may result in atrioventricular block. Accordingly, adenosine cannot be used in the setting of heart block, sinus bradycardia and junctional rhythm, which are not uncommon during STEMI and primary PCI.[22]

Only a few studies that were conducted on epinephrine and adenosine for management of no-reflow were concerned with the long-term clinical follow up of the patient as most of the studies depended on angiographic assessment and in-hospital follow up. To our knowledge, this is the first head-to-head study comparing the long-term clinical outcome of epinephrine versus adenosine for no-reflow management. Regarding one year adverse cardiovascular events, the present study showed that MACE after 1-year of follow up was lower in epinephrine arm compared to adenosine. This result was supported by the findings of Navarese et al who reported a significantly lower 30-day MACE rate

among patients treated with intracoronary epinephrine compared to conventional treatment with or without adenosine. Furthermore, the incidence of heart failure after 1-year follow up was lower in patients who received epinephrine compared to those who received adenosine. This result is in agreement with Aksu et al[16] who showed that left ventricular volumes had decreased in a statistically significant manner compared to baseline after using intracoronary epinephrine for no reflow treatment. On the other hand, Navarese et al[17] reported a numerically lower but statistically non-significant number of heart failure events at 30 days of follow up in the epinephrine-treated group. This result may be explained by the difference in sample size as they conducted their analysis only on 14 patients receiving epinephrine while our study analyzed 81 patients receiving epinephrine for no-reflow, which gave enough power for our statistically significant results.

Limitations of our study are that the study design is observational and consequently may be subject to unknown confounders and biases. Therefore, we recommend performing large randomized double-blinded clinical trials to compare the effect of epinephrine against adenosine in no-reflow management. Given that cardiac magnetic resonance imaging is the gold standard modality to assess microvascular obstruction, we recommend studying epinephrine effect on microcirculation using cardiac MRI post-primary PCI.

In conclusion, intracoronary epinephrine administration improved immediate angiographic outcome and long-term LV systolic function in refractory no-reflow. Therefore, intracoronary epinephrine could be an effective bail out management for the refractory no-reflow phenomenon during primary PCI of STEMI patients, especially in cases of failure or contraindications to other conventional agents.

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