Propensity Matched Comparison of Clinical Outcome After Immediate Versus Staged Complete Revascularization in Patients With Acute Coronary Syndrome and Multivessel Disease

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Complete revascularization (CR) in patients with acute coronary syndromes (ACS) and multivessel disease (MVD) improves clinical outcomes compared with culprit-only revascularization, but the optimal timing for non−culprit lesions treatment remains unclear. This study evaluated patients presenting with ACS and MVD admitted between January 2015 and September 2021 at the Erasmus University Medical Center. Clinical outcomes were compared between immediate and staged CR in terms of major adverse cardiac and cerebrovascular events (MACCEs), a composite of all-cause mortality, myocardial infarction, stroke, and any unplanned revascularization. A total of 1,400 patients presenting with ACS and MVD who underwent immediate or staged CR were included in this study. Using 1/many propensity score matching without replacement, 299 patients in the staged CR group were matched to 598 patients in the immediate CR group (mean 1:2 ratio), rendering a total of 897 patients for analysis. The median follow-up period was 648 days. MACCE rate was significantly higher in the staged CR group than in the immediate CR group (adjusted hazard ratio [95% confidence interval] 1.60 [1.05 to 2.45], p = 0.03). Furthermore, number of stents, stent length, and contrast usage were significantly greater in the staged revascularization group. Immediate CR was associated with less risk of MACCE than was staged CR. Staged CR required overall more contrast and stent material. **(Am J Cardiol 2023;202:6−11)**

A large proportion of patients presenting with acute coronary syndrome (ACS) have multivessel disease (MVD).[1−5] Complete revascularization (CR) results in less risk of cardiac death and myocardial infarction (MI) than does culprit-only revascularization in patients presenting with ST-elevation myocardial infarction (STEMI) and MVD.[6] The optimal CR strategy in terms of timing remains unclear.[7] Recent studies have suggested that CR also improves clinical outcomes in patients presenting with non−ST-elevation ACS (NSTE-ACS), reducing mortality and repeat revascularization.[8,9] The SMILE (Survival of Myocardial Infarction Long-term Evaluation) study showed that immediate CR might reduce the rate of major adverse cardiovascular and cerebrovascular events (MACCEs) compared with staged CR.[10] Given the lack of large randomized controlled trials (RCTs), current guidelines do not specify whether immediate CR or staged CR is the recommended strategy. Therefore, the aim of this study is to evaluate the optimal timing for CR by comparing clinical outcomes in patients with ACS and MVD treated with an immediate or staged CR strategy.

Methods

This single-center retrospective study evaluated patients presenting with ACS (STE-ACS and NSTE-ACS) and MVD who underwent a percutaneous coronary intervention (PCI) between January 2015 and September 2021 at the Erasmus University Medical Center, Rotterdam, The Netherlands. MVD was defined as ≥1 significant lesion (>70% diameter stenosis or positive physiology testing) in a non−culprit coronary artery with a vessel diameter ≥2.5 mm as assessed by visual estimation.

Exclusion criteria were out-of-hospital cardiac arrest, cardiogenic shock, presence of chronic total occlusion, previous coronary artery bypass grafting, unclear culprit, and incomplete data. Follow-up data were collected until November 2022. The population was divided into 2 groups, according to the revascularization strategy: immediate complete multivessel PCI (PCI of the culprit artery and PCI of ≥1 non−culprit artery at the index procedure with no further planned revascularization) and staged complete multivessel PCI (PCI of the culprit artery at the index procedure

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See page 10 for Declaration of Conflict of Interest.

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followed by planned revascularization of ≥1 non−culprit artery within 6 weeks). CR was achieved if all significant lesions suitable for revascularization were treated with residual percentage diameter stenosis <30% and a final thrombolysis in MI (TIMI) flow grade 3; otherwise, it was considered an incomplete revascularization.

The primary end point was MACCE defined as the composite of all-cause mortality, MI, stroke, and any unplanned revascularization,[11] whichever occurred first.

MI was defined as clinical evidence of acute myocardial ischemia and detection of an increase and/or decrease in cardiac-specific enzymes values with ≥1 value above the ninety-ninth percentile of the upper reference limit and with the presence of ischemic symptoms, or new ischemic electrocardiographic changes, or development of pathological Q waves, or evidence of new loss of viable myocardium, or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.[12] In patients whose cardiac troponin values were already elevated or recently elevated, new ischemic symptoms of the duration of at least 20 minutes and new ischemic electrocardiogram (ECG) changes are required. These ECG changes must be distinct from the original MI and not due to the usual ECG evolution of this event. Stroke was defined as any central nervous system injury or type 3a neurological dysfunction according to the NeuroARC classification (type 1 to 3a).[13] Unplanned revascularization was defined as any revascularization that occurred outside of the planned treatment modality. An earlier staged procedure was only considered an event if the patient presented with dynamic electrocardiography changes and/or a new increase of cardiac-specific enzymes values. Data on mortality were obtained through municipal civil registries up to November 2022. Clinical follow-up information was collected through letters including a questionnaire asking for MACCE and permission of the patient to request information from other hospitals, if necessary, also up to November 2022. Owing to an expected limited size of the staged group and expected differences in baseline characteristics, a propensity score matched analysis was conducted for the comparison of the immediate with the staged group. An optimal matching without replacement method was used with a ratio of 1/k (1 being staged), with k being a variable number between 1 and 3. The propensity score was estimated using a logistic regression of the treatment on covariates, including gender, age, presentation (unstable angina, NSTE-ACS, STEMI), smoking, diabetes, dyslipidemia, hypertension, family history of coronary artery disease, previous MI, previous PCI, peripheral artery disease, chronic obstructive pulmonary disease, and 3-vessel disease at presentation. Supplementary Figure 1 shows the final number of matched and discarded patients. After matching, all the standardized mean differences were <0.05, indicating adequate balance (Supplementary Figure 2). Distributions of continuous variables were tested for normality using the Shapiro-Wilk test. Continuous variables are presented as median with the twenty-fifth and seventy-fifth percentiles. Categorical variables are presented as counts and percentages. Differences in baseline characteristics in the nonmatched groups were tested using a 2-sample *t* test or Mann−Whitney *U* test for continuous variables and chi-square test for categorical variables. After patients were matched, a complete case analysis with (generalized) linear mixed models with random intercepts to account for clustering of matched patients was used to compare differences in patient-level variables. The Kaplan−Meier method was used to plot event-free survival curves for MACCE and its individual components all-cause mortality, unplanned revascularization, MI, and stroke. Estimates of the hazard ratios and 95% confidence intervals were calculated using Cox proportional hazards models. To account for the matching, the standard errors of the resulting estimates were adjusted using the grouped jackknife variance estimate. We adjusted for procedural characteristics that were statistically significant and for those that were clinically relevant. Overall, a 2-sided p value <0.05 was considered statistically significant. Data were analyzed using IBM SPSS Statistics software version 28 (IBM Corp, Armonk, New York) and R version 4.2.1 (http://www.r-project.org, *packages: MatchIt, lme4, nlme, ggpubr, plyr, data.table, dplyr, survminer, ggplot2, MASS, survival, splines, lattice, JM, ggsci*).

Results

From January 2015 to September 2021, 1,400 consecutive patients presenting with ACS and MVD who underwent immediate or staged CR were included in this study.

Baseline and procedural characteristics are reported in Table 1. At baseline, the median age of the patients was 66 years (interquartile range 56 to 73); 675 were male (75.3%); 327 were smokers (36.5%); 143 had diabetes (15.6%); 298 had dyslipidemia (33.1%); and 387 had hypertension (23.1%). STEMI was present in 540 of the patients (60.2%), non-STEMI in 293 of the patients (32.7%), and unstable angina in 64 of the patients (7.1%). Bifurcation lesions and severely calcified lesions were similarly distributed between the 2 groups, but the staged CR group had more frequently TIMI 0 to 1 flow at presentation. A total of 897 patients were successfully propensity matched in a mean 1:2 ratio, with 299 patients in the staged group being matched to 598 patients in the immediate group (Supplementary Figure 1). The absolute standardized mean differences were <0.05 for all the variables, indicating no evidence for disparity between the groups (Supplementary Figure 2 and Supplementary Table 1). Complete follow-up was available for 95% of the patients. The median follow-up period was 648 days (twenty-fifth and seventy-fifth percentiles: 371 to 942). The absolute number of events was 49 in the immediate CR and 40 in the staged CR. Cumulative incidence of MACCE at 648 days of follow-up was 15.1% for the staged and 9.5% for the immediate group. The hazard ratios for MACCE and its components for staged versus immediate CR are shown in Table 2. There were no missing values. There was a significantly greater risk of MACCE in the staged CR than in the immediate CR (Figure 1). No significant differences were detected in terms of all-cause mortality, MI, stroke, and repeat unplanned revascularization (Figure 2). In addition, we performed a subgroup analysis for STEMI and NSTE-ACS separately (Table 3, Supplementary Figures 3 and 4). The analysis of patients with STEMI showed a statistically significant difference in MACCE between the immediate and staged CR (p = 0.03), which was mainly driven by any unplanned revascularization. There was no significant difference in the patients with NSTE-ACS (p = 0.47).

Table 1
Baseline and procedural characteristics for immediate versus staged CR

Characteristics	Immediate CR (N=598)	Staged CR (N=299)	P Value
Age − years (25th-75th percentile)	66 (56-73)	65 (57-72)	1.00
STEMI − no. (%)	344 (57.5%)	196 (65.5%)	0.85
Male − no. (%)	450 (75.3%)	225 (75.3%)	0.96
Smoking − no. (%)	218 (36.5%)	109 (36.5%)	0.92
Diabetes − no. (%)	100 (16.7%)	43 (14.4%)	0.71
Dyslipidemia − no. (%)	200 (33.4%)	98 (32.8%)	0.95
Hypertension − no. (%)	259 (43.3%)	128 (42.8%)	0.88
Family history of CAD − no. (%)	184 (30.8%)	100 (33.4%)	0.50
History of MI − no. (%)	57 (9.5%)	24 (8.0%)	0.75
History of PCI − no. (%)	89 (14.9%)	43 (14.4%)	0.98
History of PAD − no. (%)	27 (4.5%)	11 (3.7%)	0.52
History of COPD − no. (%)	18 (3.0%)	7 (2.3%)	0.76
Culprit vessel			<0.001
Left main − no. (%)	13 (2.2%)	2 (0.7%)	<0.001
Left anterior descending − no. (%)	220 (36.8%)	77 (25.8%)	<0.001
Left circumflex − no. (%)	152 (25.4%)	81 (27.1%)	0.59
Right coronary artery − no. (%)	213 (35.6%)	139 (46.5%)	0.002
Bifurcation − no. (%)	195 (32.6%)	91 (33.1%)	0.51
Severe calcification − no. (%)	100 (16.7%)	50 (16.7%)	0.98
Thrombolysis in MI pre 0-1 − no. (%)	293/591 (49.6%)	177 (59.2%)	0.008
Thrombolysis in MI post 2-3 − no. (%)	593/596 (99.5%)	294 (98.3%)	0.10
Complications index procedure* − no. (%)	25 (4.2%)	6 (2.0%)	0.1
Physiology assessment: FFR − no. (%)	97 (16.2%)	79 (26.4%)	<0.001
Index intracoronary imaging: OCT and/or IVUS either pre- or post-PCI − no. (%)	105 (17.6%)	88 (29.4%)	<0.001
Index stent number − no. (25th-75th percentile)	3 (2-4)	1 (1-2)	<0.001
Index stent length (mm) − no. (25th-75th percentile)	62 (44-91)	34 (23-54)	<0.001
Total stent number (index+/-staged) − no. (25th-75th percentile)	3 (2-4)	4 (3-5)	<0.001
Total stent length (mm) (index+/-staged) − no. (25th-75th percentile)	62 (44-91)	84 (58-117)	<0.001
Index contrast (ml) − no. (25th-75th percentile)	150 (115-200)	110 (80-150)	<0.001
Total contrast (ml) (index+/-staged) − no. (25th-75th percentile)	150 (115-200)	220 (170-280)	<0.001
Complete revascularization − no. (%)	577 (96.5%)	294 (98.3%)	0.13
P2Y12 Inhibitor prescribed			
Clopidogrel − no. (%)	76 (12.7%)	26 (8.7%)	0.09
Ticagrelor − no. (%)	382 (63.9%)	183 (61.2%)	0.44
Prasugrel − no. (%)	125 (20.9%)	86 (28.8%)	0.01

* Complications include periprocedural dissections, perforation and no reflow.

An increased amount of contrast was used in the staged versus immediate group, 220 (170 to 280) and 150 (115 to 200) ml, respectively (p <0.001). The staged group also received a larger number of total stents, causing an increased total stent length of 84 (58 to 117) versus 62 (44 to 91) mm (p<0.001). The locations of the culprit lesions (left main, left anterior descending artery, and right coronary artery), the TIMI flow (0 to 1), and use of fractional

Table 2
Comparison of the cumulative incidence between revascularization strategies at 648 days

EVENT	Staged CR versus Immediate CR			
	HR [95% CI]	P value	Adjusted HR [95% CI]	P value
Major adverse cardiac and cerebrovascular events	1.65 [1.08 − 2.51]	0.02	1.60 [1.05 − 2.45]	0.03
All-cause mortality	0.81 [0.41 − 1.60]	0.55	0.79 [0.40 − 1.55]	0.50
Myocardial infarction	1.62 [0.78 − 3.38]	0.20	1.51 [0.75 − 3.05]	0.25
Any unplanned revascularization	1.62 [0.94 − 2.78]	0.08	1.63 [0.95 − 2.81]	0.08
Stroke	0.68 [0.14-3.31]	0.63	0.55 [0.12 − 2.64]	0.46

Data are presented as Hazard ratio (HR) [95% Confidence Interval (CI)] p-value. Hazard ratios were adjusted for culprit lesion vessel and thrombolysis in MI at presentation.

Dyslipidemia was defined as total cholesterol > 5.2 mmol/L, LDL-C ≥3.4 mmol/L or triglycerides ≥1.7mmol/L. Hypertension was defined as blood pressure ≥ 140/90 mmHg (millimeters of mercury). Categorical data are presented as counts and % and tested by χ^2 or Fisher's exact test when appropriate. Continuous data are presented as median and 25th to 75th percentile and tested by Mann-Whitney U test.

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CR = complete revascularization; FFR = fractional flow reserve; IVUS = intra vascular ultra sound; MI = myocardial infarction; OCT = optical coherence tomography; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

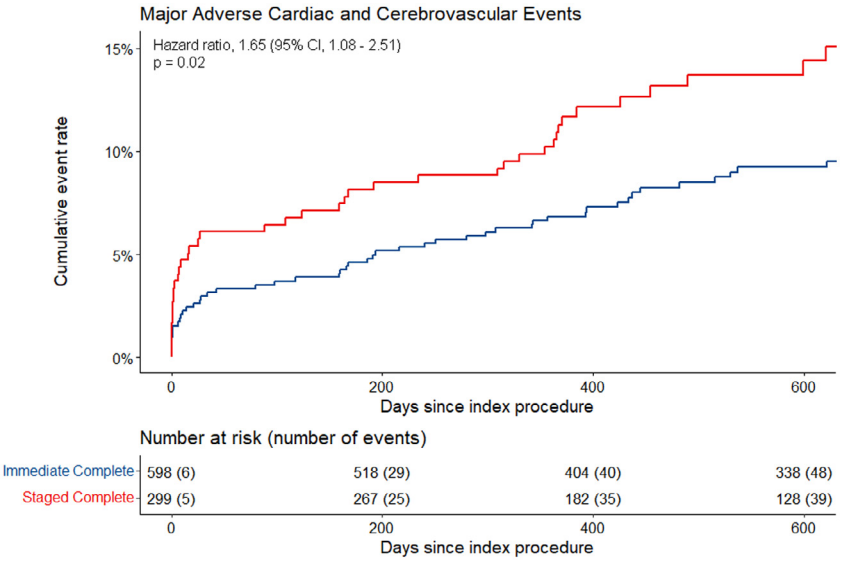

Figure 1. Kaplan−Meier curve for MACCE comparing immediate with staged CR. CI = confidence interval.

flow reserve differed significantly between the immediate and staged groups (Table 1).

Discussion

To the best of our knowledge, this study is the first to compare immediate with staged CR among patients presenting with both STE-ACS and NSTE-ACS and MVD. Our main findings are (1) immediate CR was associated with lower risk of MACCE compared with staged CR, and (2) patients in the staged group received a greater number of stents with a larger total stent length than did patients in the immediate group, and an increased total amount of contrast.

Our findings showed that immediate CR might cause less risk of MACCE in patients presenting with ACS and MVD. Interestingly, our subanalysis suggests that immediate CR

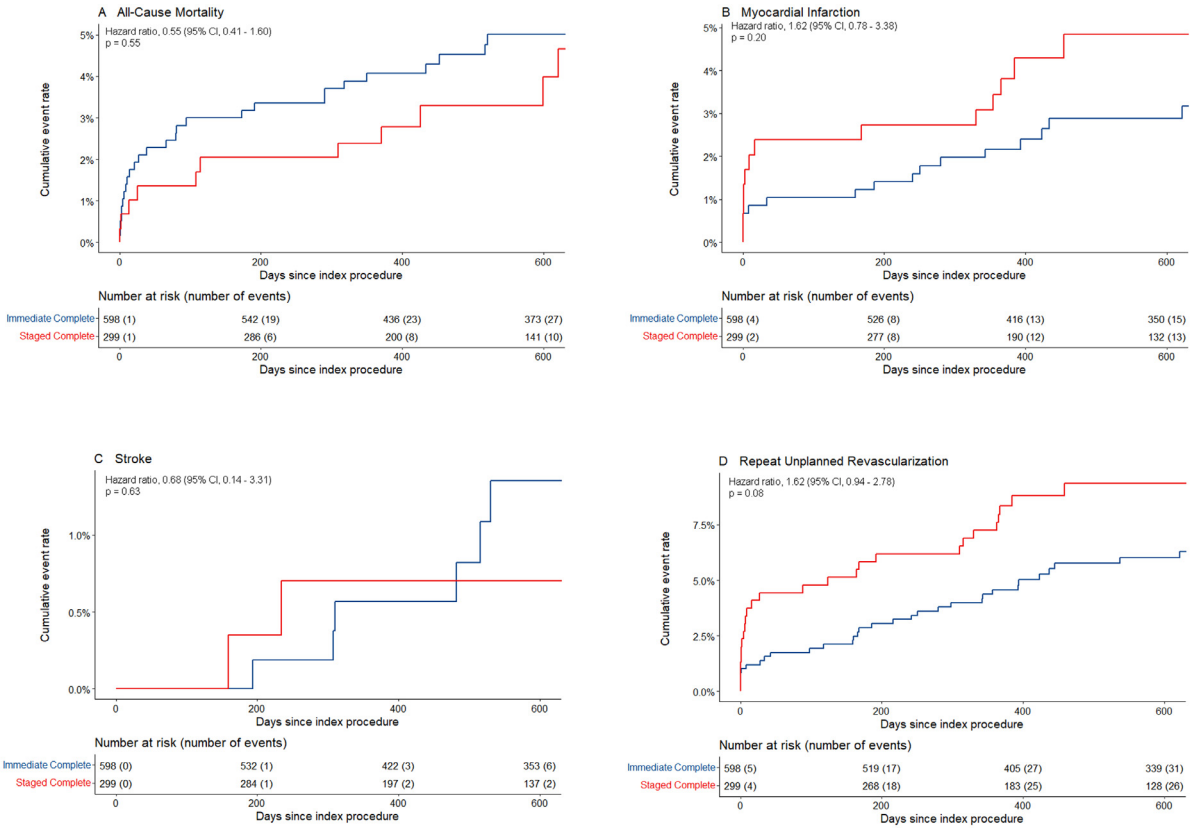

Figure 2. Kaplan−Meier curves for secondary endpoints. *A*: all-cause mortality, *B*: myocardial infarction, *C*: stroke, *D*: repeat unplanned revascularization. CI = confidence interval.

Table 3
Comparison of the cumulative incidence between revascularization strategies at 648 days in the STEMI and NSTE-ACS subgroup

EVENT	Staged Complete vs. Direct Complete			
	STEMI		NSTE-ACS	
	HR [95% CI]	P value	HR [95% CI]	P value
All-cause mortality, myocardial infarction, any unplanned revascularization and stroke	1.77 [1.07-2.93]	0.03	1.34 [0.61-2.96]	0.47
All-cause mortality	0.73 [0.25-2.07]	0.55	0.99 [0.40-2.44]	0.98
Myocardial infarction	1.76 [0.70-4.41]	0.23	1.32 [0.38-4.62]	0.66
Any unplanned revascularization	2.08 [1.10-3.90]	0.02	0.95 [0.34-2.65]	0.93*
Stroke	0.70 [0.14-3.62]	0.70	N.A.†	N.A.†

Data are presented as Hazard ratio (HR) [95% Confidence Interval (CI)] p-value.
* Proportional hazards assumption was violated.
† The event rate was too low (0.56%) and therefore no HR was calculated.

might improve clinical outcomes in patients with STEMI, reducing any unplanned revascularization compared with staged CR, whereas statistical significance could not be established in patients with NSTE-ACS. No RCTs directly investigated the immediate versus staged revascularization modalities in patients presenting with STEMI; nevertheless, a meta-analysis of RCTs showed immediate CR in patients with STEMI is associated with a lower risk of MACCE, also mainly driven by repeat revascularization. Moreover, no significant difference was found in mortality and MI.[14,15] The difference in MACCE rate was driven mainly by early events. In the staged group, a larger number of total stents were implanted than in the immediate group, with an increased total stent length. A larger number of stents and excess in stent length could increase the risk of stent-thrombosis and restenosis, possibly causing more repeat revascularization, longer hospitalization, and greater health-costs.[16,17] Similarly, a staged CR strategy, implying 2 procedures, leads to more costs but might also lead to a longer hospital admission, also increasing costs.[18] The overall use of contrast was greater in the staged group. Large contrast volume is associated with an increased incidence of contrast-induced nephropathy and mortality after PCI; however, it remains unclear whether the time interval between the contrast administration during the index and during the staged procedure might mitigate its clinical impact.[14,19,20] Given the limited available evidence, the current guidelines recommend that CR should be attempted in patients with ACS and MVD. However, the timing for CR, immediate or staged, is not clearly specified; immediate CR may be considered in patients with NSTE-ACS and MVD (recommendation class IIb, level of evidence B), but there is not enough evidence to support it in a routine and systematic fashion.[21] Similarly, in patients with STEMI, guidelines report that immediate CR should be considered in absence of cardiogenic shock recommendation class IIa, level of evidence A), but no clear recommendation is reported.[3]

A theoretical advantage of a staged procedure is the presence of recovery time between index and staged procedure. The acute setting is associated with myocardial injury and prothrombotic and proinflammatory milieu, which may increase procedural risks. Sufficient recovery time may reduce these risks.[22–24] A patient-tailored approach might be the appropriate treatment for patients with ACS and MVD. The present investigation suggests that an immediate CR strategy is safe and might improve clinical outcomes; however, there might be patients who benefit from a staged procedure. The recently published BIOVASC (Immediate versus staged complete revascularisation in patients presenting with acute coronary syndrome and multivessel coronary disease) trial showed that immediate CR is noninferior to staged CR in terms of MACCE.[25] This is a single-center, retrospective observational study. Possible case-selection bias and differences in baseline characteristics are the main limitations, even though we performed a propensity score matching to account for these issues. The clinical end point in any unplanned revascularization might be more prone to data-processing bias. There was no independent adjudication of clinical events. To confirm our data and for adjusting variables that might have confounded the results, a large, randomized trial is ongoing.

In conclusions, immediate CR was associated with less risk of MACCE than was staged CR. A staged CR strategy required overall more contrast and more stent material.

Declaration of Competing Interest

Dr. Diletti reports a relation with Erasmus Medical Center that includes funding grants. Dr. Daemen reports a relation with Erasmus Medical Center that includes consulting or advisory, funding grants, and speaking and lecture fees. Dr. Van Mieghem reports a relation with Erasmus Medical Center that includes funding grants. The remaining authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2023.05.066.

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