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REVIEW

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# Extracorporeal Life Support and New Therapeutic Strategies for Cardiac Arrest Caused by Acute Myocardial Infarction - a Critical Approach for a Critical Condition

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## Abstract

This review summarizes the most recent developments in providing advanced supportive measures for cardiopulmonary resuscitation, and the results obtained using these new therapies in patients with cardiac arrest caused by acute myocardial infarction (AMI). Also detailed are new approaches such as extracorporeal cardiopulmonary resuscitation (ECPR), intra-arrest percutaneous coronary intervention, or the regional models for systems of care aiming to reduce the critical times from cardiac arrest to initiation of ECPR and coronary revascularization.

**Keywords**: cardiac arrest, intra-arrest PCI, cardiopulmonary resuscitation

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## Introduction

Acute myocardial infarction (AMI) continues to represent a major issue for the healthcare system, being associated with a high mortality rate. In spite of the introduction of new therapies for acute coronary syndromes (ACS), the mortality associated with ACS remains as high as 20-30% [1]. Newer treatments, from primary percutaneous interventions in the emergency settings to therapeutic hypothermia in the post-resuscitation care and stem cell therapy in the post-infarction period, have significantly improved the prognosis of these patients [2,3]. Primary percutaneous intervention (PCI), performed within twelve hours from the onset of symptoms, has been demonstrated to represent the most efficient therapy for recanalization of obstructed coronary arteries and to decrease the AMI-related mortality to 3-5% in high-performance centers [4]. However, PCI can be performed only in patients who arrive in time in the catheterization laboratory. One of the major complications of AMI is represented by cardiac arrest, that can occur at home, immediately after the onset of symptoms, and before the patient is taken to a PCI center.

Sudden cardiac arrest (CA) is associated with extremely high mortality rates, which have remained high despite the major progress in the development of new therapies. The outcome for patients suffering an out of hospital cardiac arrest (OHCA) remains poor compared to patients with in-hospital cardiac arrest (IHCA), the latter having the advantage of rapid initiation of cardiopulmonary resuscitation (CPR) and early access to advanced support therapies [5,6].

Despite the significant recent progress in decreasing both the mortality and the rate of neurological alterations following CA, the survival rate after CA remains poor. Therefore, new advanced supportive strategies

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are required to further improve the success rates following resuscitation for CA in all patient categories, including AMI patients.

New supportive strategies include the use of devices for mechanical chest compression (mechanical resuscitation), that provides assistance for a more effective resuscitation in cases with prolonged duration, and devices for extracorporeal cardiopulmonary resuscitation (ECPR), that ensure the maintenance of circulation and perfusion of vital organs.

This review summarizes the most recent developments in providing advanced supportive measures for cardiopulmonary resuscitation, and the results obtained using these new therapies in patients with cardiac arrest caused by AMI. Also, new approaches for AMI patients are presented such as the concept of ECPR, intra-arrest percutaneous coronary intervention, or the regional models for systems of care aiming to reduce the critical times from cardiac arrest to initiation of ECPR and coronary revascularization.

## ■ Extracorporeal Life Support in Critical Care

### Extracorporeal life support – a therapeutic alternative

The Extracorporeal life support (ECLS) was first suggested in 1976 as a therapeutic alternative for refractory cases of cardiac arrest unresponsive to CPR [7-11]. The ECLS is used at present as an adjuvant therapy for conventional CPR, to increase the survival rate post-CPR. Table 1 summarizes the survival rates associated with ECPR reported by different clinical studies in various clinical settings. In a recent study, survival and neurologic outcomes were superior in ECPR group at 30 days after resuscitation as compared to conventional CPR [12].

The concept of ECPR is based on utilization of an extracorporeal membrane oxygenation (ECMO) system, which includes a membrane oxygenator connected to a centrifugal pump and a heat exchanger, interconnected via a bypass which is inserted percutaneously into the femoral artery and vein [13]. In patients with shock or cardiac arrest, insertion of such a veno-arterial extracorporeal membrane oxygenation system can be extremely useful in providing rapid circulatorysupport, and medical staff should be trained to set up and initiate the ECMO device within ten minutes [13].

Recent progress in medical technology has led to a significant reduction in the size of the devices used for ECLS, making it possible to bring the device to the patient place in cases of out-of-hospital cardiac arrest (OHCA) [13]. However, the results encountered when using ECLS in OHCA patients continue to be inferior to those recorded in patients with in-hospital cardiac arrest (IHCA) [14].

ECPR was considered an attractive concept for treating patients with IHCA, in whom the results obtained using ECLS are significantly superior to those obtained using conventional CPR. Several studies have reported that ECPR results in haemodynamic stabilization, increased rate of return of spontaneous circulation (ROSC), improved neurologic outcomes and improved survival compared to conventional CPR [12]. However, it is important to remember that ECPR only ensures the circulatory support for critical cases, providing an adequate blood flow to vital organs before a ROSC is achieved; it does not treat the disease which led to cardiac arrest [15].

### ECPR- who, when and to whom?

A survey including 70 centers performing ECPR indicated that cannulation is usually performed by cardiothoracic surgeons while almost all interventions are conducted by a mixed interdisciplinary team including critical care specialists, surgeons, perfusionists, and pharmacists. This survey also indicated that most of the centers do not have a well-defined list of inclusion/ex-

**Table 1. ECPR survival rates reported in clinical studies**

| Author | Patient population | n | Survival rate | Endpoint |
|---|---|---|---|---|
| Kim et al [43] | OHCA | 55 | 30% | Survival to discharge |
| Beurtheret et al [56] | Refractory CS | 104 | 36.8% | Survival to discharge |
| Yamada et al [54] | OHCA | 688 | 5.9% | 90-days survival rate |
| Kagawa et al [52-52] | Intra-arrest PCI and ECPR | 86 | 36% | Survival to discharge. |
| Yannopoulos et al [67] | OHCA | 27 | 55% | Survival to discharge |
| Sharma et al [66] | OHCA | 195 | 46.2% | Survival to discharge |
| Le Guen et al [7] | OHCA and refractory CA | 51 | 4% | 30-days survival |

*OHCA = out-of-hospital cardiac arrest, IHCA = in-hospital cardiac arrest, CA = cardiac arrest, CSA = cardiogenic shock clusion criteria when selecting a patient for ECPR [16]. Generally, it is recommended that the interdisciplinary team should be activated in order to decide whether or not to initiate ECPR in patients who do not present with any sign of a return of spontaneous circulation (ROSC) after ten minutes of advanced cardiac life support [17].

According to the current recommendations, ECPR is indicated in cases when vital signs are still present during CPR or when cardiac arrest is secondary to intoxication or hypothermia, in patients with no-flow duration less than five minutes and when the time from conventional CPR to ECPR is less than one hundred minutes [18].

Several of the criteria proposed for including a patient in an ECPR program are: ventricular fibrillation recorded on the initial electrocardiogram, a time interval of fewer than fifteen minutes from cardiac arrest until the initiation of resuscitation, presumed ischemic aetiology, and ROSC not achieved within twenty minutes of the initiation of conventional CPR [13,14].

However, the current guidelines state that there is insufficient evidence to recommend routine use of ECPR in patients with CA, this method being indicated mainly in cases when the suspected aetiology is potentially reversible after the cardiorespiratory support, but only in those settings when this can be rapidly implemented [19].

### Ethical issues related to ECPR

The ethical issues associated with the use of ECPR were recently addressed in several publications which concluded that ECPR should be considered first, before the commencement of any organ donation procedure, due the risk of including a patient in an organ donation protocol when the patient might have been saved by the use of ECPR [20,21].

### In-hospital vs. out of hospital ECPR

There is growing evidence that ECPR could be beneficial especially for IHCA patients while the results are less favorable for patients who develop CA out of a hospital setting [22]. Several studies demonstrated the ECPR is associated with significantly better results in in-hospital CPR than in out-of-hospital CA [6,23-32]. This is probably due to the faster decision time and the more rapid initiation of ECPR, following the decision in IHCA patients.

In a meta-analysis, including 38.160 patients and neurological outcomes as endpoints, ECPR showed significantly better results than conventional CPR for in-hospital patients, while for out-of-hospital CA patients the difference between ECPR and standard CPR was not statistically significant [33]. In another study on 955 patients with in-hospital or out-of-hospital CPR, IHCA patients presented a significantly higher rate of survival discharge as compared to OHCA patients ($p<0.0001$) [34]. In a 5-years long study of ECPR for refractory OHCA, the percentage of patients who were successfully weaned from the system reached 11.7% while only 8.8% of patients survived to discharge [35]. All these data indicate that ECPR represents a viable alternative especially in critical cases when CA occurs in hospitalized patients.

### Neurological outcomes after ECPR

Neurological outcomes after CA are key determinants of the future prognosis and quality of life in these critical patients [35-40]. In a study on 171 patients refractory to conventional CPR who underwent emergency cardiopulmonary bypass, insertion of intra-aortic counterpulsation pump and PCI, induction of therapeutic hypothermia at $34^0$C for 3 days, a collapse-to-bypass time of 55.5 minutes and a bypass-to-$34^0$C of 21.5 minutes were the cut off levels for predicting a favorable neurologic outcome [41].

In a small study on 24 patients with refractory CA treated with ECPR, satisfactory rates of survival good neurologic recovery were achieved in both IHCA and OHCA patients [8]. At the same time, this technique leads to rapid stabilization of the haemodynamic status in these critical patients [8,42].

In a larger study on 499 patients with CA, the transfer from conventional CPR to ECPR was associated with a better neurological outcome in patients with a duration of CPR>21 minutes, especially in younger patients, who presented without initial asystole [43]. This study demonstrated a more favorable three months neurological outcome in patients receiving ECPR than in those receiving conventional CPR when the duration of CPR was >21 minutes ($p<0.0001$). However, it is important to note that the group showing a good neurologic outcome presented a higher incidence of therapeutic hypothermia, healthy coronary arteries and lower ECPR-associated complication rates [43].

## Cardiac arrest in patient with Acute Myocardial Infarction

Acute myocardial infarction is produced by the sudden occlusion of a coronary artery, usually resulting from the rupture or erosion of a vulnerable atheromatous coronary plaque [44]. Plaque rupture or erosion often occurs at luminal sites where the percentage of coronary narrowing, as determined by coronary angiography, is not high. In 40% of victims of sudden coronary death, autopsy studies identified the location of plaque rupture at the level of a coronary lesion producing less than 50 percent diameter stenosis [45]. As a luminal narrowing of less than 50% can remain clinically silent until the moment the plaque ruptures and the subsequent formation of an intracoronary thrombosis, many of these patients can remain symptoms-free until the onset of the infarction. In such circumstances, CA can represent the first manifestation of coronary atherosclerosis and in most of these cases CA occurs out of a hospital setting. This scenario is associated with worst prognosis due to the delay in initiating appropriate supportive measures and CPR.

A recent study indicated that the primary factor associated with resistance to conventional CPR and the need to undertake ECPR was myocardial ischemia. In this study, patients who required ECPR presented an 87% rate of non-recanalization during coronary angiography compared to 58% in the nonECPR group (p=0.03) [46].

## Complex ECPR-related approaches in CA from presumed ischemic origin

A comprehensive approach in patients with reversible CA caused by acute myocardial infarction includes performance of percutaneous coronary interventions, therapeutic hypothermia to ensure neuroprotection and maintenance of organ function until recovery [47,48].

The CHEER trial studied a complex approach including mechanical CPR, ECMO initiated by critical care specialists by femoral vein and artery cannulation, therapeutic hypothermia at 33$^{0}$C for 24 hours and early reperfusion of occluded coronary arteries in patients with cardiac arrest. This trial demonstrated that a protocol instituted by critical care specialists that include ECPR, mechanical CPR, and therapeutic hypothermia is associated with a 54% survival rate with full neurologic recovery in patients with CA refractory to conventional CPR [49].

Prague OHCA study aimed to demonstrate the role of a hyper-invasive approach, including mechanical chest compression devices, cooling, ECLS and an early invasive revascularization approach, in patients with OHCA of presumed cardiac origin [50]. The preliminary results of this study showed encouraging data, with a survival rate of 20% and a cerebral performance category of 1 and 2 in 75% of survivors. However, the survival rate in patients admitted under ongoing CPR was only 30% [50].

In patients with CA caused by AMI, the post-resuscitation care should be carefully considered, including advanced measures including both reperfusion therapy and therapeutic hypothermia. When a patient undergoing ECPR is haemodynamically unstable, adjunctive steps should be rapidly initiated, including transfer to the catheterization laboratory, intra-aortic balloon counterpulsation or hypothermia induction by rapid injection of cold saline [51,52].

In OHCA patients with ventricular tachycardia/ventricular fibrillation as shown on the initial electrocardiogram, a complex treatment including ECPR, therapeutic hypothermia, and insertion of an intra-aortic balloon pump significantly improved neurological outcomes. However, in patients without pre-hospital return of spontaneous circulation, implementation of ECPR did not lead to a significantly better result [53].

In the CRITICAL registry, a Japanese network of eleven critical care centers enrolled 688 consecutive patients with OHCA, out of which only 3.0% received ECPR. This study aimed to provide the most appropriate therapeutic strategy, based on a mixed approach including PCI, cooling and ECPR for out-of-hospital cardiac arrest patients with presumed ischemic origin, preliminary data indicating very low rates of survival at 90-day and neurological performance (5.9% and 3.0% respectively) [54].

## Intra-arrest percutaneous coronary intervention

Only very few observational studies addressed the role of primary PCI in CA patients, indicating that a combined approach including ECPR and PCI may improve the outcomes of patients with refractory CA [51,52,55].

In a study including 86 patients with ACS unresponsive to conventional CPR, intra-arrest PCI was performed in 71% of the cases, leading to the return of spontaneous heart beat in all the cases. In those who survived 30 days, the rate of intra-arrest PCI was higher (p=0.04) and the time interval from CA to initiation of ECPR was shorter (p=0.002). In this study, insertion of an intra-aortic balloon pump was undertaken in 83% of cases while mild therapeutic hypothermia was indicated in only 37% of cases. Patients who received intra-arrest PCI had more favorable outcomes, such as a superior ROSC rate (p<0.001), a higher percentage of weaning from ECMO (p=0.009), a superior 30-days survival rate (p=0.03) and better neurological outcomes (p=0.005) [51,52]. This study demonstrated that intra-arrest PCI plus ECPR could decrease mortality in cardiac arrest patients who are unresponsive to CPR.

### ECPR in acute myocardial infarction with cardiogenic shock

In the setting of an AMI, cardiogenic shock is associated with high mortality when emergency circulatory support is not initiated in a timely and efficient manner [56,57]. In these critical cases, ECPR can serve as a bridge to transplantation, to implantation of a long-term assist device or to recovery, while insertion of an intra-aortic balloon pump can provide additional haemodynamic support during the bridging period.

In the case of cardiogenic shock and acute myocardial infarction, transportation of the patient to a highly specialized tertiary center is the key to survival. In the Cardiac-RESCUE program, eighty-seven consecutive patients with OHCA and refractory cardiogenic shock received ECPR support followed by emergency transport to a tertiary center. Thirty-two patients (36.8%) survived to hospital discharge, and the most powerful independent predictor of mortality was the initiation of ECPR (p<0.0001). Interestingly, after adjusting for confounding factors, the survival rate was not significantly different between cardiogenic shock patients with OHCA and those with IHCA [56].

## SYSTEMS OF CARE FOR CARDIAC ARREST FOLLOWING ACUTE MYOCARDIAL INFARCTION

### Regional models for implementation of ECPR

Various regional models have been proposed to implement the utilization of ECPR in CA patients, in a similar fashion to the implementation of the ST-elevation myocardial infarction (STEMI) networks, which proved to be extremely efficient in reducing STEMI-related mortality [4,58,59].

Implementation of new therapeutic approaches in the community can lead to significant improvement in the rate of survival accompanied by good neurological outcomes [60,61]. For instance, implementation of a system-wide approach to OHCA patients, including therapeutic hypothermia for comatose patients, initiation of ECPR, immediate coronary angiography in cases with presumed ischemic etiology of the cardiac arrest and urgent defibrillation at pre-hospital and hospital level increased the rate of discharge with good neurologic outcomes from 3.3% in 2009 to 8.5% in 2013 (p<0.001) [62]. Also, another study on 1128 OHCA patients enrolled between 2007 and 2011, showed that OHCA survival was significantly improved, from 5.6% to 13.01%, by the implementation of new approaches, consisting in automated external defibrillators, therapeutic hypothermia and implementation of ECPR programs for selected cases [63].

A Canadian registry on consecutive adults with non-traumatic OHCA showed that the integration of an ECPR program into an existing high-performance system of care might have a significant impact on patients outcome, with 68% of OHCA patients surviving to hospital admission and 42% surviving to hospital discharge [64,65].

A study of ECPR utilization for OHCA patients in the Maastricht region of southeast Netherlands analyzed the outcome of CA patients after implementing ECPR methods and proved that a shockable rhythm at presentation, the presence of ROSC and appropriate post-arrest care could improve the results of CA patients. In this study, the survivors' group presented more frequently with ACS (p=0.01), and benefitted to a greater extend from therapeutic hypothermia and PCI (p<0.01) [66]. In this network, average critical times encountered were 7 minutes for EMS response time, 24 minutes for the duration of advanced cardiac life support and 12 minutes for the transport to the emergency department [66].

In the Minessota study, including three emergent medical services systems which performed automated CPR and transport to an University hospital where EMCO was initiated, followed by coronary angiography and PCI, 78% of patients survived to hospital admission, and 55% survived to hospital discharge, while 50% achieved good neurologic outcomes [67]. However, it is important to note that in this study patients also received therapeutic hypothermia.

In another study, the increase in prehospital duration of CPR was associated with adverse outcomes despite the introduction of ECPR, indicating that transportation to a more definitive treatment facility should be preferred rather than pre-hospital initiation of ECPR in cases with an extended CPR duration [68].

### Critical time intervals in the ECPR networks

Similarly to the terms "door to needle" and "door to balloon" that are currently used to characterize the efficiency of a hospital-based system for treating myocardial infarction, the term "door-to-implantation" was proposed for patients with CA, to describe the time from arrival of the patient in a hospital to the time of implantation of the ECMO system in the catheterization laboratory, during PCI.

The studies demonstrated that such a "door-to-implantation" time less than thirty minutes significantly improved the survival rate at thirty days, in patients with OHCA. This time was significantly higher in non-survivors than in survivors ($p< 0.05$), being the most powerful predictor of mortality in these critical patients [69].

The ECPR was significantly more efficient when bystander CPR had been initiated and when initiation of ECPR was preceded by a short period of conventional CPR [70].

A small study of 35 patients who received ECMO failed to identify any significant difference between survivors and non-survivors regarding the time of arrest to CPR ($p=0.4$) and the time of CPR to ECMO ($p=0.5$), while the survivor group received in a significantly larger proportion coronary revascularization ($p=0.02$) [27]. However, a longer time interval from cardiac arrest to initiation of extracorporeal life support demonstrated to be associated with higher mortality rates [71].

The optimum time intervals for on-scene resuscitation have been addressed in a large study of 6571 cases, in which ROC analysis demonstrated that a cut off of sixteen minutes of resuscitation represented a good predictor of a favourable outcome. This study recommended a transport time of 8 to 24 minutes to be considered as the limits within which on-scene resuscitation should be performed [64].

## Newer developments in advanced supporting measures for CPR

### Mechanical resuscitation systems

Automated chest compression systems have been introduced as adjunctive measures in cases necessitating CPR, in an attempt to assist the rescuers in their efforts to provide consistent and sustained efficient compressions [72].

In patients with CA of presumed ischemic origin, mechanical chest compression systems have been developed to serve as a bridge to a better-quality support system such as ECPR or during transportation to the catheterization laboratory. Such devices increase regional cerebral oxygenation during resuscitation and improve neurological outcomes in successfully resuscitated patients with cardiac arrest.

Experimental data on porcine models proved that automatic chest compression does not interfere with extracorporeal life support systems that can be successfully installed during chest compression [73]. In an extensive study on 4868 OHCA patients out of which 285 received automated mechanical compression with the use of an automated external chest compression device, the device proved to be easy to use, being installed on average in thirty seconds [74].

Several new devices have been introduced to improve the SO2 and the neurological outcomes following CPR, such as load band distributing CPR. These have been shown to increase SO2 compared with the conventional technique [75]. In several countries which have developed a nationwide program for organ harvesting, all the emergency units have been equipped with devices allowing automated chest compression [7]. However, there is insufficient data to support or reject the use of these devices for mechanically assisted CPR, their validation being based mainly on observational studies [76].

### Therapeutic hypothermia and ECPR

Despite the great expectations of this therapeutic approach, the current evidence indicated no benefit from infusion of cold saline solutions in the pre-hospital setting [19,77]. Current guidelines do not recommend the routine pre-hospital cooling of patients when spontaneous circulation is established and suggest that this should remain reserved only for well-defined cases. However, the addition of therapeutic hypothermia to multiple protocols for CPR can lead to better mortality and neurological outcomes. According to the CHEER trial, a complex protocol that includes therapeutic hypothermia and ECPR results in a survival rate of 54% associated with full neurologic recovery [49]. Moreover, the addition of therapeutic hypothermia and early haemodynamic stabilization improved the neurological outcomes in patients with resuscitated CA [43].

## Predictors of survival in ECPR

Factors influencing the outcome after CPR include the duration of CPR, the initial cardiac rhythm, the etiol-

**Table 2 – Predictors of survival in ECPR**

| Author | Predictor | Characteristic |
|---|---|---|
| Lee et al [34], Haneya et al [79] | Initial cardiac rhythm | Shockable cardiac rhythm |
| Lee et al [34], Haneya et al [79] | Duration of CPR | For every 1- minute increase in CPR duration, survival decreases by 4% |
| Le Guen et al [7] | Delay to initiate ECPR | >10 minutes |
| Le Guen et al [7] | Duration of no-flow | <5 minutes |
| Lee et al [34], Haneya et al [79] | Etiology of cardiac arrest | Non-ischemic etiology |
| Flecher et al [83] | Age | <65 years |
| Lee et al [34] | IHCA | IHCA presented 2.49 better survival rate than OHCA |
| Lee et al [12] | Oliguria | >0.5 mL/kg/h in the first 24 h |
| Flecher et al [83] | Serum lactate | <12.0 mM/l |
| Anselmi et al82 | Duration of ECPR | >30 min |
| Flecher et al [83] | pH | >7 |
| Anselmi et al82 | Body temperature | Low body temperature at the time of ECPR implantation |

*OHCA = out-of-hospital cardiac arrest, IHCA = in-hospital cardiac arrest, CPR = cardiopulmonary resuscitation, ECPR=extracorporeal cardiopulmonary resuscitation

ogy of cardiac arrest, the underlying disease, or age [34,78-80]. At the same time, ACS and OHCA were significant negative risk factors for ROSC, with a ROSC rate 0.63 times lower in the ACS group as compared to the non-ACS group. The most significant predictors of survival in patients undergoing ECPR for CA are listed in Table 2.

In another retrospective study, the thirty days survival rate for OHCA was 43.5% when ECMO was initiated within ten minutes [34]. Important to note is the fact that with every one minute increase in CPR duration there is a 4%.decrease in the survival rate [34].

According to a small study of fifty-one cases with refractory cardiac arrest, factors related to low survival rates in ECPR were the delay in initiating ECPR and the no-flow duration [7]. Several studies demonstrated that oliguria during the first twenty-four hours after ECMO represented an independent predictor of mortality [12]. In another predictive model, a higher serum lactate level, an increased duration of ECPR and a low body temperature at the time of ECPR implantation, were predictors of mortality in cardiac arrest patients receiving ECPR [81,82].

## Conclusions

The survival of patients with cardiac arrest caused by acute myocardial infarction is largely dependent on the proper implementation of adequate therapeutic protocols to provide adequate circulatory support. ECPR proved to be associated with a significant decrease in mortality when performed timeously in well-selected cases.

In patients with OHCA caused by acute myocardial infarction, the key factors for a higher survival rate are a well-functioning prehospital emergency service, able to provide ECPR within several minutes and the transportation of the patient to well-qualified centers for urgent PCI.

A multidisciplinary team including cardiologists, heart failure specialists, critical care and neuro-critical care specialists should be involved in this therapeutic algorithm to ensure the proper management of these critical cases.

## Disclosure of conflict of interest

Nothing to declare

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