Abstract—Inflammation is a recognized key component of acute coronary syndromes. Such pathogenetic achievement has led to the use of inflammatory cells and proteins as prognostic markers in these syndromes. A number of markers have been proposed, including proinflammatory cytokines such as interleukin-6, interleukin-1RA, and tumor necrosis factor-α, adhesion molecules such as intracellular adhesion molecule-1 and vascular adhesion molecule-1 and markers of cell activation. Although all are of scientific interest, the clinical use of these markers is limited by their high cost, low availability, and unfavorable biological profile. Conversely, common markers of inflammation such as C-reactive protein (CRP), the prototypic acute phase protein, and to a lesser extent fibrinogen, have been proven to be reliable and important markers of risk in ischemic heart disease. CRP, in particular, has been found to be associated with short- and long-term prognosis in acute coronary syndromes, including ST-elevation myocardial infarction, and in stable angina, and to predict the risk of restenosis and major events, including death, after revascularization procedures. CRP has been consistently found to be independent from other risk factors and to have an incremental value beyond the common risk factors and biochemical markers of risk, including troponin. Whether CRP also should be used as a guide to therapy is still a matter of discussion that deserves further, properly designed studies. (Circulation. 2004;110:e560-e567.)

Key Words: AHA Scientific Statements ● inflammation ● revascularization ● angina ● risk factors

Short- and long-term prediction of risk in patients with acute coronary syndromes (ACS) is a challenging clinical problem. Despite diagnostic and therapeutic advances, the rate of event recurrence is still relatively high (in the range of 14% to 16% at 6 months1,2). The growing evidence that inflammation plays a pivotal role in the pathogenesis of most of the cases of ACS3 led to the use of inflammatory mediators as markers of risk in these syndromes.4 As consistent data have been accumulated in this area, risk prediction in ischemic heart disease and in ACS in particular represents the main use of inflammatory markers in cardiovascular medicine. More recently, sparse but intriguing data have been published suggesting that inflammatory markers may represent a marker of risk in other cardiovascular conditions.

C-Reactive Protein
A number of inflammatory mediators have been studied as markers of risk in ischemic heart disease. They are discussed separately. Although many of them are of potential clinical interest (discussed below), C-reactive protein (CRP) is the inflammatory marker most extensively assessed in prognostic studies and is an almost perfect marker of inflammation (it has a half-life of 19 hours and is neither consumed nor produced during the reaction). This is the result, in part, of analytical reasons because of the availability of high-sensitivity, relatively low-cost methods for its measurement and in part because of its biological profile."
Prediction of In-Hospital Events

Although CRP is considered more a marker of long-term prognosis than of short-term risk, pathophysiological evidence of a prothrombotic role for CRP and clinical data suggest that it may represent a valuable marker of risk in the short term as well (Figure 1). The first study specifically addressed to the assessment of the short-term predictive value of CRP in ACS evaluated the in-hospital composite rate of death, MI, recurrent ischemia, and urgent revascularization in a selected population of patients with unstable angina (UA) and negative troponin T. In this small study, CRP and to a lesser extent another acute phase protein, serum amyloid A (SAA) protein, levels significantly predicted events, because high-sensitivity CRP (hsCRP) >3 mg/L carried an 5-fold increased risk of recurrent events. This study was limited by its small population and by the inclusion of a well-characterized relatively uncommon population (high-risk features but negative troponin). Other studies that have subsequently addressed the same topic included different populations and evaluated different end points, leading sometimes to contradictory results. Some studies, including the large c7E3 Anti-Platelet Therapy in Unstable Refractory angina (CAPTURE) trial, failed to show a significantly increased risk of in-hospital events among patients with UA, non–ST-elevation myocardial infarction (NSTEMI), and elevated CRP levels or both NSTEMI and elevated CRP. Other large studies support the findings of high CRP levels as predictors of short-term mortality. Morrow et al showed a 18-fold increased risk of death among patients with UA and NSTEMI using a hsCRP determination and a cutoff of 15.5 mg/L. A significantly higher occurrence rate of refractory angina among patients with UA with levels in the fourth quartile (>6 mg/L versus the lowest, <1.2 mg/L) was described by Verheggen et al. Müller et al have assessed the prognostic role of CRP in 1042 patients with non-ST elevation ACS (NSTEACS) undergoing an early invasive strategy (within 24 hours; Table 1). The in-hospital mortality was significantly higher in patients having CRP levels >10 mg/L than in those with CRP <3 mg/L (3.7% versus 1.2%). More recently, James and colleagues have found in a large population (>7000 patients) of the Global Use of Strategies to Open Occluded Coronary Arteries IV-Acute Coronary Syndrome (GUSTO IV-ACS) trial that CRP levels >9.62 mg/L were associated with a significantly increased risk of death at 48 hours, 7 days, and 30 days. Although definite conclusions about the role of CRP in predicting in-hospital cardiac events cannot be drawn on the basis of the available data in the literature, when homogeneous groups of patients were selected and hsCRP determination was used, elevated CRP levels significantly predicted adverse events.

CRP and Long-Term Events

In patients with NSTEACS, CRP significantly predicts the recurrence of cardiac events in the mid- to long-term (Table 2). Available data have consistently demonstrated that CRP levels predict not only the composite end point of death, acute MI (AMI), recurrent angina, and the need for coronary revascularization procedures, but also the incidence of the single hard end point of death in follow-ups ranging from 90 days to 4 years. The large European Concerted Action on Thrombosis and disabilities (ECAT) study enrolled 2121 patients (>50% with unstable angina). After a 2-year follow-up, a 2-fold

![Figure 1. Percentage of events (lined bars: total events, including urgent revascularization; solid bar: death and MI) according to CRP levels in unstable angina (<0.001 total events; ns death and MI). Adapted from Ital Heart J. 2001;2:164–171.](http://circ.ahajournals.org/)

TABLE 1. Predictive Role of CRP Levels for In-Hospital Adverse Events in Patients With NSTEACS

<table>
<thead>
<tr>
<th>Population</th>
<th>Clinical Syndrome</th>
<th>Cutoff, mg/L</th>
<th>hsCRP</th>
<th>End Point</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benamer et al</td>
<td>UA</td>
<td>6</td>
<td>No</td>
<td>D/AMI/RA/UR</td>
<td>0.65 (0.17–2.05)</td>
</tr>
<tr>
<td>Ferreiros et al</td>
<td>UA</td>
<td>15</td>
<td>No</td>
<td>D/AMI/RA</td>
<td>0.83 (0.29–2.38)</td>
</tr>
<tr>
<td>Liuzzo et al</td>
<td>Class IIIb UA*</td>
<td>3</td>
<td>Yes</td>
<td>D/AMI/RA/UR</td>
<td>4.95 (1.40–17.49)†</td>
</tr>
<tr>
<td>Müller et al</td>
<td>NSTEACS</td>
<td>10</td>
<td>No</td>
<td>D</td>
<td>4.18 (1.57–10.97)†</td>
</tr>
<tr>
<td>Morrow et al</td>
<td>NSTEACS</td>
<td>15.5</td>
<td>Yes</td>
<td>D</td>
<td>18.28 (2.23–150.14)†</td>
</tr>
<tr>
<td>Oltrona et al</td>
<td>Class IIIb UA</td>
<td>3</td>
<td>No</td>
<td>D/AMI/UR</td>
<td>0.46 (0.19–1.11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D/AMI</td>
<td>1.94 (0.46–8.28)</td>
</tr>
</tbody>
</table>

RR indicates relative risk; D, death; RA, refractory angina; UR, urgent revascularization. Other abbreviations as in text.

*Includes only troponin-negative patients.

†P<0.05.
increase of coronary events was observed in patients with CRP >3.6 mg/L. Biasucci et al have assessed the 1-year prognostic role of CRP in 53 patients with severe unstable angina and negative troponin T. In a multivariate analysis including fibrinogen levels, age, diabetes, and hypertension, only CRP levels >3 mg/L at discharge were an independent predictor of new ischemic events, including death, MI, and hospitalization for unstable angina. The difference in the 1-year outcomes between patients with CRP levels <3 mg/L and >3 mg/L also remained significant when the outcome was analyzed according to medical or interventional treatment. In the Fragmin during Instability in Coronary Artery Disease (FRISC) study, >900 patients presenting with ACS were observed for 5 months and up to 48 months. In both studies, the risk of death was significantly greater for patients with CRP levels >10 mg/L. At 5 months, the risk of death was 7.5% in CRP levels >10 mg/L and 2.2% in CRP levels <2 mg/L. At 37 months, the risk of death was 16.5% in CRP levels >10 mg/L and 5.7% in CRP levels <2 mg/L. Intriguingly, in these studies CRP was independently associated with risk of death but not risk of MI at 5 and 37 months, and fibrinogen was independently associated with death and MI at 5 months but not at 37 months. In the CAPTURE study baseline CRP values were determined in 447 patients with unstable angina enrolled in the placebo group of the trial. All patients underwent a coronary intervention and were observed for a 6-month period. In a multivariate analysis (including troponin T levels), CRP emerged as an independent predictor of mortality at 6 months. Moreover, patients with elevated CRP levels (>10 mg/L) had a relative risk >2 of having urgent 30-day revascularization procedures, nonurgent procedures, and incidence of AMI. Müller and colleagues have assessed the prognostic role of CRP in 1042 patients with NSTEMI undergoing an early invasive strategy (within 24 hours). The patients were studied for a mean period of 20 months and up to 4 years. In this study, patients with CRP levels >10 mg/L at entry had >4 times the risk of death during follow-up.

The Müller et al and CAPTURE studies introduce the topic of the prognostic role of CRP in the presence of invasive procedures. Once again, all studies are consistent in demonstrating that in ACS patients the rate of recurrence of events, the risk of death, or both are consistently increased if preprocedural CRP is elevated, as was first shown by Buffon et al. Similar results have been published by Chew et al in >700 patients (56% of which were unstable) with a relative risk of 30-day mortality of 23.11 (95% CI 2.86 to 186.54; P<0.001) in patients with CRP >10 mg/L (fourth quartile; Table 3). Versaci et al have found a 60% recurrence of events in patients with unstable angina and preprocedural CRP levels >5 mg/L treated by coronary stenting (versus 3% among patients with CRP levels <5 mg/L, P<0.001). No MI or death occurred among patients with low CRP levels. Walter and colleagues have observed a significant and independent increase of risk after stent implantation in patients with elevated CRP levels (>5 mg/L) in a pooled population of patients with AMI, UA, and stable angina. Acute thrombotic complications were observed only in patients with elevated CRP levels, confirming the original observation by Buffon et al. De Winter and coworkers have assessed the rate of coronary events in a population of 1458 patients undergoing coronary angioplasty for stable angina or UA. Also in this relatively low-risk population, CRP levels >3 mg/L were associated with a 4.4-fold increased risk of death and MI at 14 months. No significant difference was found among patients with high versus low CRP levels in a study assessing its prognostic role in patients undergoing directional atherectomy. A higher recurrence rate also was reported in patients with high CRP levels undergoing coronary artery bypass surgery.
Prognostic Value of CRP in Relationship to Other Prognostic Markers

CRP is an independent marker of risk in all of the studies referred to in this article, but the association of CRP and troponin is of particular interest. Because CRP is an acute phase reactant and its levels increase after myocardial damage, it is not surprising that CRP levels are elevated in patients with elevated troponin levels. As first shown by Morrow et al9 and subsequently confirmed by several other studies,11,19,20,28 not only is the prognostic value of CRP independent from troponin levels, but the association of CRP and troponin levels also gives incremental prognostic information (Figure 2). In particular, in all of these studies, patients with low CRP (<110 mg/L) and negative troponin T or I have a mortality rate as low as 0% up to 4 years, whereas troponin-negative but CRP-positive patients have a significantly higher (>2%) mortality rate. These data suggest that CRP should be assessed as soon as possible and included in the risk stratification of patients with ACS. Recently, Bholasingh and colleagues18 showed that in troponin-negative patients admitted to the emergency department with chest pain but not unstable disease, a CRP level <3 mg/L was associated with a 4.5-fold increased risk of death, MI, and rehospitalization. Indeed, negative troponin and CRP might justify a no-hospitalization or early-discharge strategy, avoiding invasive procedures in these patients because they are at low risk (close to 0%) up to 48 months.18 These data and these conclusions are strengthened by a recent study by James et al,14 in which CRP was significantly associated with the risk of death (but not of new MI) at 48 hours, 7 days, and 30 days. Patients with low troponin T (<0.01 µg/L) and CRP (<1.84 mg/L) had a 30-day rate of death/MI of 2.4% versus 12.5% in those with CRP >9.62 mg/L and troponin T <0.49 µg. Zebrack et al29 have found that the predictive value of CRP is independent of coronary artery disease (CAD) extension, as evaluated by a score in 2554 patients with angina. In this study, CRP and CAD independently and additively contributed to the risk prediction: low CRP and the lowest CAD score were associated with the lowest risk, and high CRP (>10 mg/L) and the highest CAD score were associated with the highest risk, with a 10-fold difference between extremes (2.5% versus 24%).29 A new approach to risk stratification by biochemical markers has been explored by Sabatine and colleagues,30 who have assessed the prognostic value of CRP, troponin I, and B-type natriuretic peptide in 450 patients in the Orbofiban in Patients with Unstable Coronary Syndromes-Thrombolysis In Myocardial Infarction (OPUS-TIMI) 14 study and in 1635 patients in the Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction (TACTICS-TIMI) 18 study. CRP remained an independent marker of risk of death at 30 days, although the combination of the 3 markers more accurately predicted risk. A similar approach has been studied by James and coworkers in the GUSTO IV population.31 These authors have found that CRP remained a significant predictor of death, but not of MI, at 1 year, when N-terminal-pro-brain natriuretic peptide and creatinine also were considered; however, the best prediction of risk was given by the combination of the latter 2. Although the role of renal insufficiency–related factors in cardiovascular risk is still unclear, Zebrack and colleagues32 have confirmed their role but also the independent value of CRP in predicting the risk of death/MI in 1484 patients at a mean follow-up of 3 years. Intriguingly, Bazzino et al33 have suggested that CRP levels at discharge are more sensitive to

<table>
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<tr>
<th>Population</th>
<th>Clinical Syndrome</th>
<th>Cutoff, mg/L</th>
<th>hasCRP</th>
<th>End Point</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buffon et al21</td>
<td>121</td>
<td>UA (57%)</td>
<td>8</td>
<td>Yes</td>
<td>AMI/CR</td>
</tr>
<tr>
<td>Chew et al22</td>
<td>727</td>
<td>UA (56%)</td>
<td>3</td>
<td>Yes</td>
<td>D/AMI</td>
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<td>Heeschen et al11</td>
<td>447</td>
<td>NSTEMI</td>
<td>10</td>
<td>Yes</td>
<td>D/AMI</td>
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<tr>
<td>Muller et al13</td>
<td>1042</td>
<td>NSTEMI, 70% revascularized</td>
<td>10</td>
<td>No</td>
<td>D</td>
</tr>
<tr>
<td>Patti et al46</td>
<td>73</td>
<td>UA (49%)</td>
<td>6</td>
<td>Yes</td>
<td>D/AMI</td>
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<td>Versaci et al23</td>
<td>62</td>
<td>Class IIIb UA</td>
<td>5</td>
<td>No</td>
<td>D/AMI/RA</td>
</tr>
<tr>
<td>Walter et al24</td>
<td>276</td>
<td>UA (51%)</td>
<td>5</td>
<td>No</td>
<td>D/AMI</td>
</tr>
</tbody>
</table>

CR indicates clinical recurrence; other abbreviations as in Table 1.

*P<0.05.
†RR not calculated.

Figure 2. Incremental value of CRP (open bars) beyond troponin T levels (solid bars). Adapted from Am J Cardiol. 1999;84:595–598.
and specific about new coronary events than the predischarge effort stress test in NSTEACS.

CRP and ST-Segment-Elevation AMI

Although no large study has prospectively assessed the value of CRP for the prognostic short- and long-term stratification of patients with ST segment elevation AMI (STEMI), many data suggest that CRP may be of value in these patients. CRP levels in the fourth quartile were an independent predictive factor for the composite end point in 64 patients presented by Tommasi et al. Nikfardjam et al have prospectively studied 729 patients presenting with AMI and followed for 3 years. A 2-fold increase in risk of mortality was found in patients with CRP levels in the upper quintile (>10 mg/L; versus the others), but this association was less evident when correction for other parameters was made. Peak CRP levels during in-hospital course of AMI have clinical implications, predicting cardiac rupture and mortality. In experimental AMI models, human CRP binds to damaged cells, activates complement, and enhances infarct size, playing a central role in mediating cellular damage during prolonged ischemia. In the Cholesterol and Recurrent Events (CARE) study, >700 patients with previous AMI (>2 months) were studied in a long-term follow-up. Recurrence of cardiac events was almost 3-fold greater in the highest (>6.6 mg/L) versus the lowest quintile (<1.2 mg/L). In the Thrombogenic Factors and Recurrent Coronary Events (THROMBO) study, CRP was associated with 2 years' risk of recurrent events, but this association was lost after adjustment with a number of other biological markers. On average, CRP seems to maintain its prognostic value after STEMI; however, the data are not consistent and this may be because of the different population studied (few studies with STEMI; however, the data are not consistent and this may be because of the different population studied). SAA was not found to be associated with long-term risk in the NSTEACS. Other Inflammatory Markers

A number of studies have assessed the role of other markers of inflammation in ischemic heart disease. Although extensively studied, these markers on average failed to demonstrate a consistent advantage over CRP for risk prediction in ACS, stable ischemic heart disease, and revascularization procedures. Fibrinogen was consistently found to be associated with long-term risk; however, the power of this association differs among studies, probably because of nonreproducible analytical methods or because of the consumption of fibrinogen during the acute phases. In addition, adhesion molecules and proinflammatory cytokines have been associated with a risk of new coronary events in ischemic heart diseases (ie, intracellular adhesion molecule-1 and soluble vascular adhesion molecule-1) and tumor necrosis factor-α) and with clinical recurrence of symptoms. Biological, economic, and analytical reasons, as reported before, partially explain their limitations.

More recently, however, interesting studies have redefined the role of some of these markers in ischemic heart disease. SAA was not found to be associated with long-term risk in the ECAT study and to be only marginally associated by Biasucci et al. A similar association of CRP and SAA with events was also found by Morrow et al. These findings have been confirmed recently by Johnson et al in 704 women with CAD. In this study in particular, SAA but not CRP was associated with the extension of CAD. Both had a similar association with events, suggesting a possible different role of these acute phase proteins in the pathogenesis of atherosclerosis but not in the prediction of future events. IL-18 is a recently described cytokine, originally described as interferon-γ-inducing factor, that also has been described in plaques. IL-18 has been shown to be associated with future cardiovascular death in a 3.9-year-long follow-up of patients with stable angina and UA. Although independent from CRP, its prognostic value was similar to that of CRP, suggesting that IL-18 does not add significant information to that provided by CRP. Other markers seem to have the ability to add prognostic or diagnostic information or both in ischemic heart disease beyond CRP because they are supposed to be more specific for plaque activation and vascular inflammation.

Pregnancy-associated plasma protein A (PAPP-A) is a protein associated with plaque activity and morphology in ACS. PAPP-A and its endogenous inhibitor, the proform of eosinophil major basic protein, are related to complex stenosis morphology in patients with stable angina pectoris. PAPP-A levels >10 mIU/L were found to identify ACS with a sensitivity of 89% and a specificity of 81%, but the study population was small. A larger population was studied by Lund and colleagues, who found a strong correlation between PAPP-A and the combined end point death-MI-revascularization at 6 months in 200 patients with ACS. In this study, PAPP-A was also an independent marker of risk but no comparison between the 2 was made. In addition, placental growth factor-1 has been reported to be a specific marker of vascular damage and a sensitive marker of future events in the large number of patients with ACS from the CAPTURE study. Recently, there has been a renewed interested in myeloperoxidase, a proinflammatory leukocyte enzyme that is abundant in ruptured plaque. Myeloperoxidase has been found to be associated with the recurrence of events in a large population of emergency department patients with chest pain but negative troponins and in a population of ACS patients from the CAPTURE study. Intriguingly, myeloperoxidase was independent of both troponin and CRP levels. Although the potential for studying markers directly associated with plaque growth and rupture is intriguing, studies enrolling larger populations are needed before any of these markers can be considered of clinical use.

Immunologic Markers

Recently, Biasucci and coworkers showed that seropositivity for Chlamydia pneumoniae (Cp) heat shock protein 60 (HSP60), a protein of the superantigen family sharing 85% homology with human HSP60, is present in 99% of patients with ACS versus 20% of patients with effort stable angina and 0% normals. This protein appears to be a promising diagnostic tool because no other marker has yet been reported to be present in 99% of UA, with 99% in sensitivity and specificity for the presence of disease. Cp HSP60 seroposi-
CRP Determination: Implication for Therapy

The strong association of CRP with prognosis and its role in the pathogenesis of ischemic heart disease raise the possible role of CRP as a guide to conventional or antiinflammatory therapy. Although no randomized controlled trial has explored this issue, some suggestions can be drawn from retrospective analysis. Patients with low CRP and troponin levels have a highly favorable prognosis. Mortality among these patients is extremely low and therefore the assumption of a reduced need for aggressive therapy in this group appears reasonable. Targeting drug therapy based on CRP levels was shown to be effective in primary prevention trials. Interestingly, the medical therapies known to be effective in the treatment of ACS (eg, aspirin, clopidogrel, abciximab, statins) appear to lower cardiac risk together with CRP levels or to be effective only in patients with high CRP.60–63 Definite conclusions cannot be drawn at this point and randomized controlled trials are needed to clarify these issues, but the idea that CRP may be used as a guide to therapy is fascinating and reasonable.64

Other Cardiovascular Diseases

Data are accumulating on the possible prognostic role of CRP or other inflammatory markers in cardiovascular disease that are different from pure ischemic heart disease. Rossi et al have observed a nearly 5-fold increase in the risk of death and MI in a population of patients with severe peripheral vascular disease with CRP levels >11.7 mg/dL (third tertile versus the others). In congestive heart failure, consistent data have been presented on the role of tumor necrosis factor-α, TNF soluble receptors, and interleukin-6. More recently, CRP levels have been found to have a prognostic value in the occurrence of sudden death and the persistence of atrial fibrillation. Although intriguing, these studies await further confirmation.

Conclusions

In conclusion, available data strongly recommend the use of CRP as a prognostic marker in patients with ACS in addition to other prognostic factors, including troponin levels. Other inflammatory markers, including SAA, fibrinogen, and proinflammatory cytokines, although frequently reported to be associated with prognosis in cardiovascular diseases, are supported by less consistent data and have biological, economic, and analytical limitations. In almost all studies, the prognostic value of CRP was independent from that of other prognostic markers. The data are consistent for intermediate to long-term follow-up and less consistent for in-hospital outcomes. An evaluation of CRP levels at the time of admission should be included in the evaluation of the patient risk profile, including clinical data, associated diseases, markers of myocardial necrosis (especially troponin levels), left ventricle performance, and age. Although different cutoff levels have been used, the data are consistent in identifying a cutoff level of 10 mg/L as a marker of higher risk for death and possibly myocardial infarction in ACS, whereas a cutoff of 3 mg/L identifies a group of patients at intermediate risk and a high rate of recurrent events. In stable disease, a cutoff of 3 mg/L (hsCRP) is indicated. In the majority of the studies, the determination of CRP levels was made at the time of hospital admission and, therefore, admission values should be considered the reference value in estimating prognosis. In patients with chronic heart disease, samples should be taken in the quiescent phase of the disease, avoiding acute illness and repeating the measurement if CRP is elevated (>3 mg/L) to confirm the value.

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References


CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: Clinical Use of Inflammatory Markers in Patients With Cardiovascular Diseases: A Background Paper

Luigi M. Biasucci

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