Bayesian Methods Affirm the Use of Percutaneous Coronary Intervention to Improve Survival in Patients With Unprotected Left Main Coronary Artery Disease

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Background—Several randomized clinical trials support the use of coronary artery bypass grafting (CABG) for patients with unprotected left main coronary artery disease. Studies suggesting the equivalence of percutaneous coronary intervention (PCI) with CABG for this indication indirectly support the 2011 American College of Cardiology Foundation/American Heart Association Class IIa recommendation for PCI to improve survival in patients with unprotected left main coronary artery disease. We tested whether bayesian approaches uphold the new recommendation.

Methods and Results—We performed a bayesian cross-design and network meta-analysis of 12 studies (4 randomized clinical trials and 8 observational studies) comparing CABG with PCI (n=4574 patients) and of 7 studies (2 randomized clinical trials and 5 observational studies) comparing CABG with medical therapy (n=3224 patients). The odds ratios of 1-year mortality after PCI compared with CABG using bayesian cross-design meta-analysis were not different among randomized clinical trials (odds ratio, 0.99; 95% bayesian credible interval, 0.67–1.43), matched cohort studies (odds ratio, 1.10; 95% bayesian credible interval, 0.76–1.73), and other types of cohort studies (odds ratio, 0.93; 95% bayesian credible interval, 0.58–1.35). A network meta-analysis suggested that medical therapy is associated with higher 1-year mortality than the use of PCI for patients with unprotected left main coronary artery disease (odds ratio, 3.22; 95% bayesian credible interval, 1.96–5.30).

Conclusions—Bayesian methods support the current guidelines, which were based on traditional statistical methods and have proposed that PCI, like CABG, improves survival for patients with unprotected left main coronary artery disease compared with medical therapy. An integrated approach using both direct and indirect evidence may yield new insights to enhance the translation of clinical trial data into practice. (Circulation. 2013;127:2177-2185.)

Key Words: coronary disease • meta-analysis • stents
thought to be the most objective process for guideline development, is usually but not always limited by the conflation of P values with treatment benefits, equal weights attached to different types of studies, and difficulty in updating existing beliefs with new information.28

Recognizing the challenges inherent in guideline development, members of the ACCF/AHA Task Force on Practice Guidelines sought to determine whether a bayesian approach, which incorporates clinical judgment through prior distributions and establishes inferences based on probability functions, would provide new insights into the development of clinical practice guidelines beyond the current approach based on traditional statistical inference. This article illustrates the use of bayesian cross-design and network meta-analyses to compare the relative effectiveness of CABG, PCI, and MT for patients with ULMCAD and describes how bayesian methods may inform the process of guideline development.

Methods
A review of the 2011 PCI guideline and Data Supplements 3 and 4 revealed that 4 randomized trials13–16 and 8 cohort studies17–24 comprised the evidence for the new Class IIa recommendation for PCI to improve survival in patients with ULMCAD, whereas 7 older studies formed the knowledge base to show that CABG confers a survival advantage over MT in patients with ULMCAD.23–26 The 19 studies used predefined enrollment criteria and were published in peer-reviewed journals. Two independent reviewers (Y.H. and J.A.B.) extracted the following data: sample size, length of follow-up, clinical events (death at 1, 2, and 3 years), study design (randomized, observational matched cohort, observational cohort), study and subject age, and the proportion of male subjects. The primary end point of the present analysis was all-cause mortality at 1 year.

Traditional (Frequentist) Meta-Analysis
The traditional statistical meta-analytic approach involved 2 common strategies: a fixed-effects and a random-effects meta-analysis.27 In the fixed-effects model, an estimate of the summary odds ratio (OR) significantly larger than 1 implied that PCI was associated with a higher 1-year mortality than CABG. Because all the primary studies were conducted by different investigators at different times and had different designs, the variation between studies was also estimated in a random-effects model, and such variation was incorporated into the estimation of the summary effect.27

Bayesian Meta-Analyses
Traditional meta-analysis, which summarizes treatment effects across multiple clinical trials, usually weights each study by its sample size and thus provides a single inference for the treatment-effect average across all populations in the analysis. A bayesian cross-design analysis can weight evidence from disparate sources differently to determine whether treatment effects vary, for example, between randomized clinical trials (RCTs) and cohort studies. A bayesian network meta-analysis can make indirect comparisons among multiple treatments (CABG versus PCI versus MT) when direct comparisons do not exist (PCI versus MT). In the present investigation, we compared the statistical inferences from bayesian meta-analyses with those from traditional frequentist approaches in patients with ULMCAD.

In each of the 19 studies23–26,15–24 a CABG arm was observed. We assumed that the number of deaths in the CABG arm arose from a binomial distribution and that the log-odds of the study-specific CABG mortality rate had a noninformative normal prior distribution. For the 12 studies that directly compared CABG with PCI,23–25 we assumed that the number of deaths in the PCI arm was also a binomial variable with the log-odds of the study-specific PCI mortality rate modeled as the rate for the CABG surgery arm plus a study-specific increment associated with the PCI arm. The study-specific effect attributed to PCI was assumed to arise from a normal distribution with unknown mean and unknown PCI-specific between-study variance. Similarly, for the 7 studies that directly compared CABG surgery with MT,23,24 we assumed that the number of deaths in the MT arm was a binomial variable with the log-odds of study-specific MT mortality modeled as the rate for CABG surgery arm plus a study-specific increment for the MT arm. As above, the study-specific MT effect was assumed to arise from a normal distribution with unknown mean and unknown MT-specific between-study variation. We permitted the between-study standard deviation of the MT effects and of the PCI effects to arise from independent uniform distributions. This permitted the between-study variation to differ between the PCI arms and the MT arms. Using pooled estimates, we computed the posterior median for the OR of death after PCI versus CABG and after MT versus CABG, along with 95% bayesian probability intervals (commonly called credible intervals). An indirect estimate of the OR of death from MT versus PCI was also computed from model parameters.

Accounting for Study Age
In an additional analysis, we down-weighted older studies. We assumed that the most recent study comparing CABG with MT was more comparable to contemporary patient selection and treatments than the older studies and therefore imposed a ratio of 3 for the ratio of the prior probability distributions to reflect the relative weight between the current and older studies. Additional sensitivity analyses changing that ratio were performed.

Statistical Software
Models were estimated via programs written with WinBUGS (http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml) statistical software for bayesian analysis and used Markov chain Monte Carlo methods.

Results
Bayesian Cross-Design Analysis of Studies Comparing PCI With CABG
The 12 studies that met the selection criteria to compare 1-year mortality after revascularization with either PCI or CABG in patients with ULMCAD included 4 randomized trials,13–16 4 matched cohort studies,17–20 and 4 other types of observational studies (Table 1).21–24 We first used a hierarchical bayesian model for the comparative effectiveness between PCI and CABG, imposed noninformative priors so that the posterior inference would be dominated by the likelihood of the data, and observed that the posterior median for the summary OR was 1.04 and the 95% bayesian credible interval (BCI) was 0.74 to 1.39. Because the interval included 1, the results showed no significant difference between the 2 treatments for 1-year mortality.

In the cross-design synthesis analysis, we adopted a strategy to incorporate the systematic differences of the different study designs.27 In such analyses, we imposed prior distributions or constraints to the random-effects models to reflect our prior opinions about the designs. Examples included the premise that estimates from RCTs might be less biased than estimates from observational studies and that more weight should be assigned to the evidence from RCTs than that from other studies. We observed that the ORs of 1-year mortality after PCI compared with CABG using bayesian cross-design meta-analysis were not different among the 3 study types (Figure 1): RCTs (OR, 0.99; 95% BCI, 0.67–1.43), matched cohort studies (OR, 1.10; 95% BCI, 0.76–1.73), and other types of cohort studies (OR, 0.93; 95% BCI, 0.58–1.35).
Comparison of Bayesian and Frequentist Meta-Analyses: PCI Versus CABG

Bayesian analysis of all 12 studies from the cross-design meta-analysis (Figure 1) yielded a median of the posterior distribution for the summary OR of 1.01 (95% BCI, 0.68–1.45). We compared this finding with that obtained from the traditional frequentist approach, which pooled all 12 studies in both a fixed-effects and random-effects meta-analysis and suggested no statistically significant difference between PCI and CABG in 1-year mortality (Figure 2). This fixed-effects meta-analysis yielded a pooled OR estimate of 1.03 (95% confidence interval, 0.81–1.32), and the random-effects meta-analysis yielded a pooled OR of 1.00 (95% confidence interval, 0.72–1.40).

Bayesian Network Meta-Analysis to Compare PCI With MT

In the absence of randomized trials comparing 1-year mortality after PCI and MT, we performed an indirect analysis using a network meta-analysis (Figure 3). Using summary data from trials comparing CABG and MT (Table 2), we first performed a traditional frequentist random-effects meta-analysis (Figure 4). The summary mortality OR for MT relative to CABG across all studies was 3.33 (95% CI, 2.63–4.23). Because all studies had the CABG arm (Table 3), we then pooled the primary studies comparing PCI with CABG and MT with CABG to obtain indirect comparisons between PCI and MT. Some studies had the PCI treatment arm but no MT arm, whereas others had the MT arm but no PCI arm (Figure 3). From the former studies, we obtained the summary treatment effect between PCI and CABG, and from the latter, we obtained the summary treatment effect between MT and CABG. The indirect estimate for the difference between PCI and MT was obtained as the difference between the 2 summary effects. In other terms (parametrized by the difference in the log-odds), PCI−MT=(PCI−CABG)−(MT−CABG). The results of the network meta-analysis suggested that PCI confers a survival benefit compared with MT for patients with ULMCAD (Figure 5).

Longer-term follow-up data at 2 and 3 years from the 19 studies were limited,2–8,13–24,28 and using data extracted from survival plots might be less accurate or precise than using tabular data. Despite this, we found no significant differences between PCI and CABG and significant advantages of PCI over MT from the indirect comparisons (Table 4). This is consistent with the results from using 1-year mortality data in support of the relevant recommendation.

Accounting for Older Studies

The above analysis assumed that the difference between MT and CABG surgery was observed in mostly older studies. When we assigned 3 times more weight to the evidence from the more recent study by Dzavik and colleagues8 than to the older studies, we obtained similar results for 1-year mortality for PCI versus CABG (posterior median OR, 0.96; 95% BCI, 0.58–1.40), MT versus CABG (posterior median OR, 3.22; 95% BCI, 2.22–4.56), and MT versus PCI (posterior median OR, 3.46; 95% BCI, 2.00–6.22). Sensitivity analyses varying such weights in a reasonable range show similar conclusions.
Study-Level Characteristics
To explore whether CABG alone was the common factor affecting outcomes in the comparisons with PCI and MT, we identified possible confounders (proportion of male subjects, average age of participants, and year of first randomization) that differed across the treatment arms and might affect the primary end point (Table 3). We observed that CABG participants used as comparators against MT patients were more likely to be young or male in contrast to CABG participants compared against PCI patients (Figure 6). We also observed that CABG participants used as comparators against MT patients tended to undergo CABG before 1996, whereas CABG participants used as comparators against PCI patients underwent surgery after 1996 (Table 3).

Discussion
The 2011 ACCF/AHA CABG and PCI practice guidelines10,12 state the following:

*PCI to improve survival is reasonable as an alternative to CABG in selected stable patients with significant (≥50% diameter stenosis) unprotected left main CAD with: 1) anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (eg, a low SYNTAX score ≤22, ostial or trunk left main CAD); and 2) clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (eg, STS-predicted risk of operative mortality ≥5%). (Class of Recommendation IIa; Level of Evidence, B).*

To achieve consensus for recommendation, 39 cardiologists and cardiac surgeons qualitatively extrapolated evidence from a broad range of sources. In the absence of a trial directly comparing PCI with MT, the writing committee downgraded the Level of Evidence from A to B. After peer review, the ACCF/AHA Task Force approved the Class IIa recommendation with Level of Evidence B,10,12 consistent with the earlier recommendation by the ESC/EACTS.11

In the present analysis, we applied bayesian methods to assess the evidence for the main stem of the recommendation, which claims that PCI improves survival in selected patients with ULMCAD. The analysis produced several findings. First, the network meta-analysis suggested that PCI is superior to MT in patients with ULMCAD, in support of the revascularization guideline. Second, bayesian cross-design meta-analysis suggested the equivalence of CABG and PCI for patients with ULMCAD by generating a posterior median OR of 1.01 (95% BCI, 0.68–1.45), which is numerically similar to the result of OR of 1.00 (95% confidence interval, 0.72–1.40) obtained with frequentist random-effects methods and suggests that there is a chance that the use of PCI for ULMCAD could be associated with a 40% increase (or 28% decrease) in 1-year mortality compared with CABG.

Although the point estimates and intervals generated by the frequentist and bayesian methods are numerically similar, the interpretation of the 2 outputs is quite different.29 The frequentist approach defines probability as a limit as the number of trials approaches infinity and therefore measures a frequency or rate. The true value for the OR may or may not lie within the 95% confidence interval. In other words, the probability that the true value for the OR lies within the confidence interval of 0.72 to 1.40 is either 0 or 1. That is, it either does or does not lie within the specified confidence interval.

On the other hand, the bayesian method generates a credible interval that has a high probability of containing the true OR. In other words, the true value for the OR has a 95% probability of lying within the interval of 0.68 to 1.45. Because the value 1 is included in the credible interval, which is also quite symmetrical, the results show no evidence of a difference between PCI and CABG for 1-year mortality. The possibility that PCI is associated with different 1-year mortality than CABG is extremely small (<2.5% for a possible 45% increase or for a 32% decrease, according to the definition of the 95% BCI).

Reliability of the Cross-Design Meta-Analysis
In the cross-design analysis, we observed that the ORs for 1-year mortality after PCI or CABG were similar across a range of study types. In the rules for guideline development, evidence from RCTs and meta-analysis is assigned to Level
of Evidence A, and data from a single RCT or multiple observational studies are assigned to Level of Evidence B. This seems reasonable because patient populations for RCTs may be more homogeneous, the between-study variance for RCTs smaller, inferences less biased, and the point estimates for outcomes more accurate than those from observational studies. On the other hand, cohort studies probably reflect real-world practice more than RCTs. In any case, these judgments are prior beliefs rather than facts, and our analysis suggests that RCTs and cohort studies produced similar results and conclusions for 1-year mortality rates after PCI or CABG for ULMCAD after incorporating these prior beliefs using bayesian methods.

Validity of the Network Meta-Analysis
The validity of the network meta-analysis depends on several factors. The original trials should be sufficiently homogeneous; trial subjects should have similar baseline characteristics; and the treatments used in each trial should be similar. Relevant to the present analysis, it would be ideal to determine that patients enrolled in the CABG arms of the CABG-versus-MT trials are similar to those enrolled in the CABG arms of the CABG-versus-PCI trials. However, we identified significant heterogeneity in baseline characteristics among the trials in the network meta-analysis. Subjects in the early studies were predominantly male with a median age of 50.8 years, whereas subjects in SYNTAX had a more balanced sex distribution with median age of 65.1 years. Furthermore, it would be ideal to determine that medical treatments were similar across all studies. However, the CABG-versus-MT studies took place in the 1960s and 1970s before several improvements in MT such as dual antiplatelet therapy, statins, angiotensin-converting enzyme inhibitors, and improved anti-ischemic medications took place. We attempted to address this by up-weighting the most recent study by Dzavik and colleagues. However, that study was published in 2001 and reflected MT before many advances were in common use. Although methods are available for adjusting for changes in patient characteristics or treatments that have occurred across studies in a network analysis, significant limitations exist, and the inability to control for secular changes is a recognized limitation of the network meta-analysis.

When we adjusted for study age, our analysis suggested that the benefit of revascularization with either CABG or PCI was maintained over MT over the time course of the studies performed. Adjusting for the other covariates is challenging because of the fewer number of studies that report these covariates. We have run some meta-regressions including these factors as sensitivity analyses. Despite the wide credible intervals for the ORs obtained as a result of a lack of statistical power, we do not find evidence that these factors confound the indirect comparisons. On the other hand, several unreported covariates such as the use of aspirin, statins, or internal mammary artery grafting would likely influence mortality rates in the trials and could be incorporated into regression analyses if they had been measured and available for analysis.

Longer Follow-Up
The present analysis defined 1-year mortality as the primary end point because this hard outcome was available in all 19 studies in the revascularization guidelines. Some, but not all, studies reported longer follow-up results. It is recognized that indirect comparisons performed in a network meta-analysis may give misleading results when trial numbers are small. For this reason, we consider the primary analysis using the 1-year mortality data to be supportive of the existing revascularization guidelines and the additional 2-year and 3-year mortality analyses to be sensitivity analyses.
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Generalizability of Results
The use of PCI for ULMCAD is increasing in everyday practice. Data from the ACC–National Cardiovascular Data Registry from 417 institutions showed that PCI for ULMCAD increased from 17% to 22% between 2002 and 2004, whereas CABG decreased from 83% to 78%.33 In a run-in analysis for the SYNTAX study,30 PCI for ULMCAD with or without 3-vessel disease was performed in the United States in 18% of cases and in Europe in 29% of cases.34

Although the present study evaluated an important end point, the clinical heterogeneity of ULMCAD limits the generalizability of the results. Approximately 80% of patients with ULMCAD have additional characteristics unfavorable for PCI.35 Lesion location determines the technical feasibility of PCI for ULMCAD. Treating the ostium or trunk is more straightforward than treating distal lesions involving the bifurcation or trifurcation. In a registry analysis,36 the cumulative incidence of death, myocardial infarction, or target vessel revascularization after a median follow-up of 587 days was significantly higher in patients with distal disease than in those with proximal or midsegment LMCAD (30% versus 11%; hazard ratio, 3.42; 95% confidence interval, 1.34–9.7; P=0.007). Because of technical considerations, the writing committees of ESC/EACTS11 and the ACCF/AHA10,12 applied a Class IIa recommendation for ostial or trunk disease and maintained a lower Class IIb recommendation for distal bifurcation disease (“may be considered”). For revascularization decisions for patients with ULMCAD or complex multivessel CAD, the writing committees assigned a Class I recommendation to CABG to improve survival and recommended the use of the heart team approach,10–12 even in situations of clinical equipoise.

Table 3. Combined Evidence Tables

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CABG indicates coronary artery bypass surgery; LEMANS, Study of Unprotected Left Main Stenting Versus Bypass Surgery; MAIN-COMPARE, Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization; MT, medical therapy; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stant in Patients With Left Main Coronary Artery Disease; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery. Values are numbers of subjects and 1-year mortalities.

Figure 5. Bayesian network meta-analysis: posterior median odds ratios (ORs) and 95% Bayesian credible intervals (BCIs) for 1-year mortality after percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or medical therapy (MT).
SYNTAX Scores
The presence of extensive coronary disease in other coronary arteries affects outcome in patients with ULMCAD. In patients with ULMCAD and SYNTAX scores ≥33, the risk of all-cause death was 9.7% after PCI and 4.1% after CABG after 1 year of follow-up (P=0.06). For the subset of patients with isolated ULMCAD in SYNTAX, mortality rates after PCI versus CABG were similar after 3 years of follow-up (7.3% versus 8.4%; OR, 0.86; 95% confidence interval, 0.59–1.24; P=0.64). For all patients with either ULMCAD or multivessel CAD, the importance of high SYNTAX scores becomes more apparent after 3 years of follow-up, because the presence of a SYNTAX score ≥33 was associated with higher rates of adverse outcomes (aside from stroke) after PCI than after CABG. On the basis of the important analyses relating outcomes to disease severity, we recognize that the inability to incorporate SYNTAX scores into the Bayesian analysis is a limitation of the present study.

Because of remaining uncertainties about the short- and long-term equivalence of PCI to CABG, additional research is needed. The EXCEL trial (Evaluation of XIENCE PRIME™ Everolimus Eluting Stent System (EECSS) or XIENCE V® EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NCT01205776) is currently recruiting patients. At the present time, the majority of patients with ULMCAD in everyday practice will continue to be candidates for CABG.

Bayesian Analyses for Guideline Development
The goal of clinical decision making is to make inferences about the effect of treatment approaches when evidence comes from disparate sources or direct comparisons do not exist. In the present analysis, the Bayesian and frequentist analyses produced numerically similar point and interval estimates. If the frequentist and Bayesian analyses had produced discordant results, a more extensive sensitivity analysis would have been required to explore a potential weakness in the guidelines. As it turns out, the results of Bayesian analysis add credibility to the medical beliefs underlying the guidelines for patients with ULMCAD.

The frequentist and Bayesian methods both involve indirect comparisons and incorporate observational data and indirect assessments of outcomes based on randomized treatment allocation. Caution should be exercised, however, when statistical methods are applied to clinical guideline development. Such inferences are limited by differences among studies in design, size, age, length of follow-up, and population characteristics. Although the Bayesian analysis of the referenced studies has resulted in conclusions similar to those derived from the classic frequentist approach presented in the

Table 4. Meta-Analysis of Longer-Term Follow-Up Data

<table>
<thead>
<tr>
<th>Data</th>
<th>Frequentist PCI vs CABG OR (95% Confidence Interval)</th>
<th>Bayesian PCI vs CABG OR (95% Bayesian Credible Interval)</th>
<th>Bayesian Indirect MT vs PCI OR (95% Bayesian Credible Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-y</td>
<td>1.11 (0.79–1.56)</td>
<td>1.14 (0.82–1.57)</td>
<td>3.89 (2.50–6.13)</td>
</tr>
<tr>
<td>3-y</td>
<td>1.03 (0.75–1.42)</td>
<td>1.04 (0.62–1.66)</td>
<td>4.04 (2.39–7.72)</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; MT, medical therapy; OR, odds ratio; and PCI, percutaneous coronary intervention.
revascularization guidelines, the strength of the primary evidence might not be Elevated as a result of the lack of adequately powered, direct randomized comparisons. It is fair to say that no statistical analysis can fully unravel the confounding inherent in nonrandomized, observational data and even direct comparisons of randomized studies. This might preclude the accurate estimation of the magnitude of sometimes even the direction of the effect of an intervention. Although bayesian analysis can add insight and inform guideline recommendations, it is important not to lose sight of the fact that indirect evidence based on a mixture of disparate trials might inevitably be of lower quality than direct comparisons originating from well-executed randomized studies and hence by itself falls below the standard established by ACCF/AHA for Level of Evidence A. From a methodological perspective, therefore, we believe that the developed analytic strategies might be applied to recommendations to assist the decision making in general for the purpose of exploratory or sensitivity analyses.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

The 2011 American College of Cardiology Foundation/American Heart Association revascularization guidelines have assigned a Class IIa recommendation (“should be considered”) to percutaneous coronary intervention (PCI) to improve survival over medical therapy in selected patients with unprotected left main coronary artery disease, yet no trials have directly compared PCI with medical therapy for patients with this condition. We used traditional frequentist statistical approaches and bayesian methods to analyze the 7 trials comparing coronary artery bypass graft surgery with PCI for patients with unprotected left main coronary artery disease. An integrated approach using both frequentist and bayesian methods may yield new insights to enhance the translation of trial data into clinical practice.
Bayesian Methods Affirm the Use of Percutaneous Coronary Intervention to Improve Survival in Patients With Unprotected Left Main Coronary Artery Disease
John A. Bittl, Yulei He, Alice K. Jacobs, Clyde W. Yancy and Sharon-Lise T. Normand on behalf of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

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