The 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for patients with ST-segment–elevation myocardial infarction (STEMI) give a class III indication for nonculprit artery percutaneous coronary intervention at the time of primary percutaneous coronary intervention, driven by data from observational studies. However, more recent trials suggest otherwise.

Methods and Results—We conducted PUBMED, EMBASE, and CENTRAL searches for randomized trials comparing complete versus culprit-only revascularization in patients with ST-segment–elevation myocardial infarction. Efficacy outcomes were major adverse cardiovascular events, as well as death, cardiovascular death, myocardial infarction, and repeat revascularization. Safety outcomes were contrast-induced nephropathy, contrast volume used, and procedure time. Five trials with 1165 patients fulfilled the inclusion criteria. Complete revascularization (68% during index percutaneous coronary intervention) was associated with significant reduction in major adverse cardiovascular events (rate ratio = 0.48; 95% confidence interval = 0.37–0.61), death (rate ratio = 0.60; 95% confidence interval = 0.38–0.97), cardiovascular death (rate ratio = 0.38; 95% confidence interval = 0.20–0.73), and repeat revascularization (rate ratio = 0.42; 95% confidence interval = 0.31–0.57) when compared with culprit-only revascularization. However, trial sequential analyses (similar to interim analysis of a randomized trial) powered for a 25% relative reduction showed firm evidence (cumulative z-curve crossed the monitoring boundary) only for major adverse cardiovascular events driven by a decrease in repeat revascularization with no firm evidence for reduction in death and myocardial infarction. Moreover, there was a significant increase in contrast volume use (mean difference 85.12 [70.41–83.00] ml) and procedure time (mean difference 16.42 [13.22–19.63] mins) with complete revascularization without increase in contrast-induced nephropathy.

Conclusions—In patients with ST-segment–elevation myocardial infarction, immediate or staged complete revascularization results in significant reduction in major adverse cardiovascular events driven largely by reduction in repeat revascularization with no firm evidence for the reduction in death or myocardial infarction when compared with culprit-only revascularization. (Circ Cardiovasc Interv. 2015;8:e002142. DOI: 10.1161/CIRCINTERVENTIONS.114.002142.)

Key Words: complete revascularization

The 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for patients with ST-segment–elevation myocardial infarction (STEMI) give a class III (level B) recommendation (harm) for percutaneous coronary intervention (PCI) of a nonculprit artery at the time of primary PCI in patients without hemodynamic compromise.¹ The 2014 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines, however, give a class IIb recommendation for immediate revascularization of nonculprit artery in select patients.² Both guidelines permit PCI of nonculprit artery at a time separate from primary PCI for symptoms or for ischemia on noninvasive testing.¹² On the other hand, revascularization of a nonculprit artery during index hospitalization is considered inappropriate by the appropriate use criteria for coronary revascularization.³

The cited evidence for harm by the ACCF/AHA guideline is data from observational studies with potential selection and ascertainment biases. Since the 2013 guideline publication, 2 randomized clinical trials (RCTs) have shown a significant benefit of complete revascularization (predominantly done at the same setting as culprit artery PCI) when compared with culprit-only revascularization.⁴ In the Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial (n=465),
WHAT IS KNOWN

• Patients with ST-segment–elevation myocardial infarction and multivessel disease have significant increase in cardiovascular events.
• Guidelines largely discourage complete revascularization at the time of index percutaneous coronary intervention, but recent randomized trials seem to suggest otherwise.

WHAT THE STUDY ADDS

• Data from randomized trials indicate significant reduction in major adverse cardiovascular events, as well as a reduction in death, cardiovascular death, and repeat revascularization with complete revascularization in patients with ST-segment–elevation myocardial infarction.
• However, with a total of only 1165 patients, our analyses indicate that there is lack of firm evidence to support reduction of death and myocardial infarction.

complete revascularization at the time of culprit artery PCI was associated with significant reduction in cardiovascular outcomes when compared with culprit-only PCI, in a trial that was prematurely terminated—a result likely overestimated because of premature termination.4 Similarly, in the Complete Versus Lesion-Only Primary PCI Trial (CvLPRIT; n=296), complete revascularization at index hospitalization (27% as staged procedure) was associated with significant reduction in primary end point when compared with culprit-only revascularization.6 However, these 2 RCTs were not powered for outcomes of death and myocardial infarction (MI).

Our objective was to assess the benefit and harm of complete revascularization (same setting or staged) versus culprit-only revascularization in patients with STEMI and multivessel disease. Given the small sample size of the published trials and the dangers of overestimating effect sizes with traditional meta-analysis,7 especially in prematurely terminated trials and for outcomes which were not powered for, our objective was also to use robust methodology to critically evaluate whether the current accumulated data provides firm evidence to support complete revascularization for prevention of clinically relevant outcomes.

Methods

Eligibility Criteria

We conducted PUBMED, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) searches for RCTs using the terms complete revascularization, culprit artery revascularization, infarct-related artery revascularization, noninfarct-related artery revascularization, and MI, until November 2014 (Week 2). In addition, we searched the presentations at major cardiovascular scientific sessions and the bibliography of original trials, meta-analyses, and review articles identified to find other eligible trials.

Eligible trials had to fulfill the following criteria: (1) RCTs comparing complete versus culprit-only revascularization in patients with STEMI and (2) reporting outcomes of interest (as outlined later). The study by Politi et al8 had 3 randomized intervention arms: culprit-only revascularization, complete revascularization performed as a staged revascularization, and complete revascularization performed simultaneously at the time of culprit artery PCI. For the purposes of this analysis, both of the complete revascularization arms were combined.

Trial Selection and Bias Assessment

Two authors (B. Toklu and S. Bangalore) independently assessed trial eligibility and trial bias risk and extracted data. Disagreements were resolved by consensus. The bias risk of trials was assessed using the components recommended by the Cochrane Collaboration—allocation sequence generation, allocation concealment, and blinding of outcome assessors. For each component, trials were categorized as low, high, or unclear risk of bias. We considered trials with high or unclear risk of bias for any one of the above components as trials with high risk of bias.

Outcomes

Efficacy and safety outcomes were evaluated. Efficacy outcomes were long-term major adverse cardiovascular events (MACE), as well as death, cardiovascular death, nonfatal MI, and revascularization. Safety outcomes were contrast-induced nephropathy, volume of contrast administered, and procedure time. Other PCI-related complications (such as access-related complications) were not consistently reported across the trials.

Statistical Analyses

The meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,9,10 using standard software (Stata 12.1, Stata corporation, Texas),11 and an intention-to-treat approach. Given the variable duration of follow-up among the included trials, the analysis used the incident rate of outcomes per 1000 person-years to obtain the log incident rate ratios (RR) of one treatment relative to another treatment. Rates, rather than number of events, were used as this was considered the most appropriate for this analysis because they incorporate the duration of the trials, which was variable. A mixed-effect poisson regression model was used to calculate effect sizes.12 Poisson regression models were fitted in Stata using the glamm module. For the summary-based approach, RR was calculated using both the fixed-effect model and the random-effects model of DerSimonian and Laird.13 Heterogeneity, which is the proportion of total variation observed between the trials attributable to differences between trials rather than sampling error (chance), was assessed using the F statistic,14 with P<0.25 considered low and P>0.75 high.

Sensitivity analysis was conducted using the traditional count-based approach. In addition, a meta-regression analysis was performed to evaluate the relationship of percentage of patients with staged revascularization in the complete revascularization arm on outcomes. We used a residual maximum likelihood to estimate the additive (between-study) component of variance τ̂2 for the meta-regression analysis. Bootstrap analyses were performed using a Monte Carlo permutation test for meta-regression using 10000 random permutations.15

Trial Sequential Analysis

Cumulative meta-analyses and repetitive testing of accumulating data run the risks of producing type I and type II errors. TSA is similar to interim analyses in a single trial, where monitoring boundaries are used to decide whether a trial could be terminated early when a P value is sufficiently small to show the anticipated effect or for futility. TSA was performed using standard software (TSA ver 0.9 Beta)16 anticipating a 25% relative risk reduction for efficacy outcome, α=5% and 1−β=80% and estimating the required diversity adjusted information size. The methodology has been described previously.17,18 The 25% relative reduction was chosen because this is the nominal effect size seen in cardiovascular trials that is both clinically meaningful and realistic. For TSA, trial sequential monitoring boundaries are drawn for each outcome, similar to interim analysis of randomized trials,
Bangalore et al  Complete Revascularization for STEMI

and provides information as to whether to continue evaluating for evidence (eg, continue the COMPLETE trial) when the boundary is not crossed or whether sufficient evidence is reached for anticipated effect or for futility when the boundary is crossed. The interpretation is similar to that of DeMets stopping boundaries for clinical trials.

**Results**

Our search yielded 5 trials that enrolled 1165 patients who fulfilled the inclusion criteria (Figure 1). Among the 1165 patients, 519 (44.5%) patients were randomized to the culprit-only revascularization. Among the 646 patients randomized to complete revascularization, 68% underwent complete revascularization at the time of index PCI (Table). All trials were deemed low risk for bias (Table).

**Major Adverse Cardiovascular Events**

With 5 trials and 233 events, complete revascularization was associated with significant reduction in MACE (14.2% versus 27.2%; incident rate ratio [RR] 0.48; 95% confidence interval [CI] 0.37–0.61) when compared with culprit-only revascularization (Figure 2A). In the TSA, the cumulative z-curve crossed both the traditional boundary ($P=0.05$) and the trial sequential monitoring boundary, indicating that there is firm evidence for a 25% reduction in MACE with complete revascularization when compared with culprit-only revascularization (Figure 2B).

**Death and Cardiovascular Death**

With 5 trials and 68 deaths, complete revascularization was associated with significant reduction in death (4.5% versus 7.5%; RR=0.60; 95% CI 0.38–0.97) when compared with culprit-only revascularization (Figure 3A). However, in the TSA, the cumulative z-curve crossed the traditional boundary ($P=0.05$) but not the trial sequential monitoring boundary, indicating lack of a firm evidence for a 25% reduction in death with complete revascularization when compared with culprit-only revascularization.

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**Table. Baseline Characteristics of Included Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Sample Size</th>
<th>Follow-up (months)</th>
<th>Staged PCI for Complete Revascularization, %</th>
<th>Anterior MI (% Complete vs Culprit)</th>
<th>Stent Use (% Complete vs Culprit)</th>
<th>DES Use (% Complete vs Culprit)</th>
<th>Bias Assessment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CvLPRIT</td>
<td>2014</td>
<td>296</td>
<td>12</td>
<td>27</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>+++</td>
</tr>
<tr>
<td>Dambrink et al</td>
<td>2010</td>
<td>121</td>
<td>6</td>
<td>100</td>
<td>21 vs 29</td>
<td>93 vs 83</td>
<td>23 vs 17</td>
<td>+++</td>
</tr>
<tr>
<td>HELP AMI</td>
<td>2004</td>
<td>69</td>
<td>12</td>
<td>0</td>
<td>52 vs 59</td>
<td>100 vs 100</td>
<td>0 vs 0</td>
<td>+++</td>
</tr>
<tr>
<td>Politi et al</td>
<td>2010</td>
<td>214</td>
<td>30</td>
<td>50</td>
<td>45 vs 42</td>
<td>100 vs 100</td>
<td>8 vs 12</td>
<td>+++</td>
</tr>
<tr>
<td>PRAMI</td>
<td>2013</td>
<td>465</td>
<td>23</td>
<td>0</td>
<td>29 vs 39</td>
<td>100 vs 100</td>
<td>71 vs 58</td>
<td>+++</td>
</tr>
</tbody>
</table>

+ indicates low bias risk; CvLPRIT, Complete Versus Culprit-Lesion Only Primary PCI Trial; DES, drug eluting stent; HELP AMI, Hepacost for Culprit or Multivessel Stenting for Acute Myocardial Infarction; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention; and PRAMI, Preventive Angioplasty in Acute Myocardial Infarction.

*Represents risk of bias based on: sequence generation of allocation; allocation concealment and blinding of outcome assessor.
Complete Revascularization for STEMI

Results were largely similar for cardiovascular death with significant reduction in cardiovascular death with complete versus culprit-only revascularization (2.3% versus 5.6%; RR=0.38, 95% CI 0.20–0.73), but the TSA indicating lack of firm evidence for a 25% reduction with the accumulated information size (Figure 3C–3D).

Nonfatal MI

With 5 trials and 59 events, there was numerically lower MI with complete revascularization when compared with culprit-only revascularization, but this was not statistically significant (4.2% versus 6.2%; RR=0.64; 95% CI 0.37–1.08) (Figure 4A). There was moderate heterogeneity in the analysis (P=41%), which was explained by the Dambrink et al trial.

Exclusion of this trial showed that complete revascularization was associated with a 59% reduction in MI when compared with culprit-only revascularization (RR=0.41; 95% CI 0.23–0.76). There was no heterogeneity in this analysis. In the TSA, the cumulative z-curve failed to cross both the traditional boundary (P=0.05) and the trial sequential monitoring boundary, indicating lack of firm evidence for a 25% reduction in MI with complete versus culprit-only revascularization.

Figure 2. A, Complete vs culprit-only revascularization for the outcome of major adverse cardiovascular events (MACE).4,6,8,19,20 B, Trial sequential analysis (TSA) for the outcome of MACE. The required information size is based on an anticipated intervention effect of 25% relative risk reduction, a control event proportion estimated from the cumulated culprit-only revascularization event proportion, and a diversity =25%, α=0.05, and β=0.20. CI indicates confidence interval; CvLPRIT, Complete Versus Culprit-Lesion Only Primary PCI Trial; HELP AMI, Hepacoat for Culprit or Multivessel Stenting for Acute Myocardial Infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; and PRAMI, Preventive Angioplasty in Acute Myocardial Infarction.
Figure 3. Continued
Repeat Revascularization
With 5 trials and 167 events, complete revascularization was associated with significant reduction in repeat revascularization (9.6% versus 20.2%; RR=0.42; 95% CI 0.31–0.57) when compared with culprit-only revascularization (Figure 5A). In the TSA, the cumulative z-curve crossed both the traditional boundary ($P=0.05$) and the trial sequential monitoring boundary, indicating that there is firm evidence for a 25% reduction in revascularization with complete revascularization when compared with culprit-only revascularization (Figure 5B).

Safety Outcomes
Contrast-induced nephropathy was rare (total 16 events) and was not statistically different between the 2 groups (RR=0.65; 95% CI 0.24–1.74). In addition, there was a significant increase in contrast volume use (weighted mean difference 85.12 ml (70.41–99.83 ml) and procedure time (weighted mean difference 16.42 mins (13.22–19.63 mins) with complete revascularization when compared with culprit-only revascularization.

Results were largely similar when the analyses were performed using counts rather than person-years of follow-up. There was low to moderate degree of heterogeneity in the above analyses without significant small study effect. Meta-regression analysis evaluating the relationship between percent of patients with staged PCI for complete revascularization showed no statistically significant relationship for most outcomes, except for a trend ($P=0.06$) toward worse outcomes for MI in trials where greater percent of patients underwent staged PCI.

Discussion
The results of this meta-analysis with data derived from randomized trials show a significant reduction in MACE and reduction in death, cardiovascular death, MI, and repeat revascularization at the expense of an increase in contrast volume use and procedure time with complete revascularization (performed at the time of index PCI in 68% of patients) when compared with culprit-only revascularization in patients with STEMI and multivessel disease. However, with only a total of 1165 patients, the current study shows that there is firm evidence only for reduction of MACE with complete revascularization, largely driven by reduction in revascularization, without firm evidence for other outcomes.

STEMI and Multivessel Disease
Data from multiple studies suggest that multivessel disease is common in patients presenting with STEMI (30% to 60%)

$^{21–23}$ and that presence of significant nonculprit lesion is associated with poor outcomes. $^{21,24}$ Despite this exponential increase in adverse outcomes, robust clinical trials to address management strategies were lacking for decades. Evidence from observational studies suggested harms of nonculprit PCI, especially if done during the same setting as culprit artery PCI. $^{23}$ Consequently, for years, most national and international guidelines considered nonculprit PCI as a class III recommendation (harm) at the time of index PCI. The class III recommendation would dictate that the occasional patient who underwent nonculprit PCI in deference to the guideline recommendation to be a high-risk patient. Observational studies using data from such high-risk patients not surprisingly showed harms of nonculprit PCI. Therefore, in the setting of a class III recommendation, data from observational studies should be viewed with caution because the guideline recommendation, if followed, itself results in serious selection bias.

Politi et al included 214 patients with STEMI and multivessel disease randomized to culprit-only revascularization
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(N=84), in-hospital complete revascularization group (N=65),
or postdischarge complete revascularization group (N=65). The sample size was calculated based on a large 66% reduction in primary outcome and therefore required only few patients. The study showed a significant benefit of the 2 complete revascularization strategies for long-term MACE driven by reduction in repeat revascularization with no mortality benefit compared with culprit-only revascularization. The PRAMI trial was designed to enroll 600 patients, powered to detect a 30% reduction in primary outcome, but was terminated early after only 465 patients were enrolled based on the recommendation by the Data Safety and Monitoring Board after a highly significant reduction in primary outcome. The PRAMI trial showed a significant reduction in primary composite outcome, as well as reduction in cardiac death and MI, nonfatal MI, and refractory angina with complete revascularization (at the time of index procedure) when compared with culprit-only revascularization. Similarly, in the CvLPRIT, complete revascularization at index hospitalization (27% as staged in-hospital procedure) was associated with significant reduction in primary end point when compared with culprit-only revascularization. None of the trials were powered for hard outcomes of death and MI. Although the trials were well conducted, outcomes such as refractory angina and urgent revascularization are problematic in an unblinded trial given the knowledge of anatomy. Given the lack of sufficiently powered trials to address patient important outcomes, we performed a meta-analysis of these trials.

The results of the study suggest a significant benefit of complete revascularization over culprit-only revascularization for

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**Figure 4. A.** Complete vs culprit-only revascularization for the outcome of myocardial infarction (MI). Calculation of required information size as in Figure 2B. CI indicates confidence interval; CvLPRIT, Complete Versus Culprit-Lesion Only Primary PCI Trial; HELP AMI, Hepacoat for Culprit or Multivessel Stenting for Acute Myocardial Infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; and PRAMI, Preventive Angioplasty in Acute Myocardial Infarction.
the reduction of MACE, as well as for the reduction of death, cardiovascular death, MI, and repeat revascularization. These results are similar to our previous meta-analysis of largely observational studies from 19 studies that evaluated 61,764 subjects with STEMI and multivessel disease where we found a significant lower risk of MACE, death, and repeat revascularization with complete revascularization compared with culprit-only revascularization.26 Bainey et al in a meta-analysis of 26 studies (23 nonrandomized) with 46,324 patients found a higher in-hospital mortality (OR=1.35; 95% CI 1.19–1.54) but a trend toward lower long-term mortality for patients undergoing complete revascularization during index procedure (OR=0.85; 95% CI 0.70–1.03), but a significant reduction in long-term mortality with either in-hospital (OR=0.48; 95% CI 0.35–0.67) or elective outpatient staged complete revascularization (OR=0.46; 95% CI 0.33–0.64) when compared with culprit-only revascularization.27 Among randomized trials, only the trial by Politi et al reported acute outcomes between the randomized arms of immediate complete revascularization versus staged complete revascularization and showed a trend toward worse in-hospital mortality (3.1% versus 0.0%) but lower rate of contrast-induced nephropathy (1.5% versus 3.1%) and shorter length of stay (4.8 days versus 5.4 days) with immediate complete revascularization.8

In our current analysis of data from RCTs, one might be tempted to conclude that complete revascularization is the way to go given significant benefits, including reduction in death and MI in the traditional meta-analysis. However, given the total sample size of 1165 patients only, trial sequential
analyses powered for a more realistic 25% relative risk reduction showed that the current body of evidence provides firm evidence only for the reduction of MACE, which is largely driven by reduction in repeat revascularization. There is no firm evidence for reduction of death, cardiovascular death, and MI. The interpretation of the TSA is similar to interim analysis of clinical trials. Here, the interim analysis is performed with every published trials and can dictate whether a sufficient level of evidence has been reached (by the cumulative \( \gamma \)-curve crossing the trial sequential monitoring boundary) or the futility boundary is reached. For outcomes of death, cardiovascular death, and MI, the cumulative \( \gamma \)-curve does not cross the monitoring boundaries, which in a randomized trial would suggest that the clinical trial should not be stopped. In a similar light, the current analyses suggest that the role of complete revascularization for reduction of hard outcomes is uncertain and needs more evidence. Prior evidence from prematurely terminated trials or subgroup analyses of randomized trials dictates the need to carefully interpret the secondary outcomes from randomized trials, especially when the trials are small. The 40%, 62%, and 59% relative reduction in death, cardiovascular death, and MI observed with complete revascularization in the current study is likely too good to be true.

The results of this study lend support to the continuation of the Complete Versus Culprit-Only Revascularization to Treat Multivessel Disease After Primary PCI for STEMI (COMPLETE) trial, which is anticipated to enroll \( \approx \)3900 patients from across the world and will be powered for hard outcomes of death and MI (ClinicalTrials.gov Identifier: NCT01740479). In addition, the trial is testing staged complete revascularization, a strategy which is different than that of the PRAMI and CvLPRIT trials. Moreover, the trial encourages second-generation drug-eluting stents and contemporary dual antiplatelet therapy with Ticagrelor and enrols both primary PCI and fibrinolysis patients.

Study Limitations

Similar to other trial level meta-analyses, there were variability in the inclusion/exclusion criteria among the studies and variability in the follow-up duration. We used a poisson regression meta-analysis to account for variability in follow-up duration, but the results were largely similar in a count base analysis. In addition, the results are applicable to the select patients enrolled in the clinical trials (largely without chronic total occlusions and left main disease) and cannot be extrapolated to other cohorts. In addition, the trials used variable proportion of drug eluting and bare metal stents. Moreover, the study addresses the question of culprit-only versus complete revascularization, but does not provide insights into the timing of completeness of revascularization, whether staged or immediate.

Conclusions

Data from randomized trials indicate significant reduction in MACE, as well as reduction in death, cardiovascular death, MI, and repeat revascularization at the expense of increase in contrast volume use and procedure time with complete revascularization (performed at the time of index procedure in 68% of patients) when compared with culprit-only revascularization in patients with STEMI and multivessel disease. However, with only a total of 1165 patients, our analyses indicate that there is firm evidence to support at least a 25% reduction only for MACE driven largely by reduction in repeat revascularization. However, there is no firm evidence to support reduction in other outcomes, including death and MI. The results of this study lend credence to the continuation of the COMPLETE trial.

Disclosures

Dr Wettlesv has been and is a member of the Copenhagen Trial Units task force for developing theory and software for trials sequential analysis (TSA). The other authors report no conflicts.

References

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Complete Versus Culprit-Only Revascularization for ST-Segment–Elevation Myocardial Infarction and Multivessel Disease: A Meta-Analysis and Trial Sequential Analysis of Randomized Trials
Sripal Bangalore, Bora Toklu and Jørn Wetterslev

Circ Cardiovasc Interv. 2015;8:
doi: 10.1161/CIRCINTERVENTIONS.114.002142
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

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