Endarterectomy vs stenting for carotid artery stenosis: A systematic review and meta-analysis

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Objectives: The relative efficacy and safety of endarterectomy and stenting in patients with carotid stenosis remain unclear. In this review we synthesize the available evidence derived from randomized controlled trials (RCTs) that compared the two procedures in terms of the risks of death, stroke (disabling and nondisabling), and nonfatal myocardial infarction.

Methods: We searched for RCTs in MEDLINE, EMBASE, Current Contents, and Cochrane CENTRAL; expert files, and bibliographies of included articles. Two reviewers, working independently, determined trial eligibility and extracted descriptive, methodologic, and outcome data from each eligible RCT. Random-effects meta-analysis was used to assess relative and absolute risks and the I² statistic was used to assess heterogeneity of treatment effect among trials.

Results: Ten RCTs with 3182 participants proved eligible. At 30 days and compared with endarterectomy, carotid stenting was associated with a nonsignificant reduction in the risk of death (relative risk [RR], 0.61; 95% confidence interval [CI], 0.27-1.37); I² = 0%), a nonsignificant reduction in the risk of nonfatal myocardial infarction (RR, 0.43; 95% CI 0.17-1.11; I² = 0%), and a nonsignificant increase in the risk of any stroke (RR, 1.29; 95% CI, 0.73-2.26; I² = 40%) and major/disabling stroke (RR, 1.06; 95% CI, 0.32-3.52; I² = 45%). If one considers the two procedures equivalent if the absolute difference in events is <2%, these results provide moderate-quality evidence for equivalence with respect to death (risk difference [RD] =-0.40, 95% CI −1.02 to 0.40) and nonfatal myocardial infarction (RD, −0.70; 95% CI −1.90 to 0.50), but because of much wider CI, only low-quality evidence of equivalence in stroke (RD, 1.00; 95% CI, −1.00 to 3.10).

Conclusion: In RCTs, carotid stenting and carotid endarterectomy seem equivalent in terms of death and nonfatal myocardial infarction. Although the impact on stroke remains unestablished, results are consistent with a clinically important increase in stroke risk with stenting, an intervention that aims at reducing the risk of stroke. (J Vasc Surg 2008;48:487-93.)

Randomized controlled trials (RCTs) have shown carotid endarterectomy (CEA) to reduce the incidence of stroke and death in symptomatic and asymptomatic patients.1,2 Carotid angioplasty and stenting (CAS) has emerged in the last decade as a feasible and less invasive alternative, particularly for patients with multiple comorbidities who may have a high perioperative risk. Although observational studies of angioplasty, later enhanced through the use of stents and cerebral protective devices, suggested that this procedure was safe and effective,3,4 several large trials have reported their findings since the aforementioned meta-analysis was published, the task force intended to evaluate the safety and the efficacy of the two procedures and identify certain populations that may derive differential benefits from the procedures, particularly, subgroups defined by the presence of symptoms, age, and perioperative risk.

METHODS

The report of this protocol-driven systematic review adheres to the Quality of Reporting of Meta-analyses (QUOROM) standards for reporting systematic reviews of RCTs.6

Eligibility criteria. We included RCTs that compared CEA and CAS (with and without the use of cerebral pro-
ective devices) in patients with carotid stenosis. The outcomes of interest were death, stroke, and myocardial infarction (MI) at 30 days and 1 year after the procedure. We included RCTs regardless of their publication status, language, size, or duration of patient follow-up.

**Study identification.** An expert reference librarian (P. J. E.) designed and conducted the electronic search strategy with input from study investigators with expertise in conducting systematic reviews. To identify eligible studies, we searched electronic databases (MEDLINE, EMBASE, Current Contents, and Cochrane CENTRAL through the Ovid interface) from 2003 through April 2007. A published rigorous systematic review provided references before October 2003.\(^8\) We also sought references from experts, bibliographies of included trials, and the Institute for Scientific Information (ISI) Science Citation Index for publications that cited included RCTs (details available from the authors upon request).

Two reviewers, working independently, screened all abstracts and titles and, upon retrieval of candidate studies, the full text publications for eligibility. Inter-reviewer agreement was adequate (κ = 0.85), and disagreements were resolved by consensus.

**Data collection.** Two reviewers, working independently and using a standardized form, extracted data from all eligible RCTs, including RCTs identified in the 2003 review, which included:

- descriptive data—study size, number of patients in each arm, patients’ age, the usage of stents and cerebral protection devices, the presence of symptoms, the length of follow-up, and the degree of stenosis;
- methodologic data—elements of bias protection such as allocation concealment, blinding, proportions of patients lost to follow-up, funding, and whether studies were stopped prematurely before reaching their planned sample size; and
- outcome data—death, major and disabling stroke, any stroke, Q-wave and non-Q wave MI.

We attempted to contact authors of all included RCTs by e-mail to obtain missing data.

**Statistical analysis**

### Meta-analyses.** We pooled relative risks (RR) from each trial using the DerSimonian-Laird random-effects model\(^7\) and estimated the 95% confidence intervals (CI) for the outcomes of death, major and disabling stroke, any stroke, and Q-wave and non-Q wave nonfatal MI. We used the I\(^2\) statistic, which estimates the percentage of total variation across studies that is due to heterogeneity rather than chance,\(^8\) that is, the percentage of variability in treatment effects across trials that is not due to chance or random error, but rather due to real differences in study patients, design or interventions. Statistical analysis was conducted by using Comprehensive Meta-Analysis version 2 software (2005; Biostat Inc, Englewood, NJ).

A key assumption in the interpretation of composite end points is that there is a common treatment effect on its components.\(^9\) We found several RCTs reporting composite end points in which the effect of treatment on the components violated the assumption of a uniform underlying treatment effect (ie, the intervention caused more strokes but less deaths). Thus, we abandoned pooling composite outcomes and pooled only the three individual outcomes of interest.

**Subgroup and sensitivity analyses.** A priori hypotheses to explain potential heterogeneity in the direction and magnitude of effect among RCTs included patient-level characteristics such as the presence of symptoms, age, gender, diabetes status, history of renal failure, a prior stroke, plaque morphology, and the severity of stenosis. In addition, we planned subgroup analysis based on trial-level characteristics such as the surgical volume of operators, the use of cerebral protection devices, and whether RCTs were stopped prematurely before reaching their planned sample size, a practice that may lead to overestimation of treatment benefits.\(^10\) We anticipated that several trials might have sparse data (zero events in one or both study arms), which leads to a risk of zero and makes calculating relative risks (risk ratios) impossible.

A standard statistical procedure is to add a very small constant to all four cells in a two × two table to facilitate ratio calculation. To ascertain the robustness of our analysis, we repeated analysis by using three other different constants (ie, three different continuity correction methods) to determine whether the choice of method affects results. The analysis reported in this article follows the treatment arm method for continuity correction, and sensitivity analyses tested three other alternative continuity correction methods (constant correction factors of 0.5 or 0.01, and the reciprocal of opposite arm size).\(^11\) In addition, we planned to conduct sensitivity analysis to determine the extent to which the inclusion of zero total events trials (trials with no events in either arm) affected pooled estimates.\(^12\)

**Equivalence analyses.** We estimated the pooled risk difference (RD) and CIs for each of the outcomes by conducting random-effects meta-analyses of RDs derived from individual trials. RCTs have used thresholds of equivalence or noninferiority for composite end points that included our outcomes of interest that were in the range of

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**Fig. 1.** Study selection. RCT, Randomized controlled trial.
Angioplasty in Patients With Symptomatic Severe Carotid Stenosis; High Risk for Endarterectomy; SPACE, patients.18 Patients in all trials were deemed candidates for comes. Only one trial exclusively recruited asymptomatic 1 to 45 months, with most studies reporting 30-day out-

The follow-up period ranged from 6 of the 10 RCTs responded to our queries and the other trials did not from only two trials,13,15 because the other trials did not receive endovascular procedures.1,3,21

**Methodologic quality.** Table II summarizes the reported methodologic quality of the included RCTs. The reviewers had adequate agreement in judging study quality (mean κ = 0.83; range, 0.71-1.0). Six trials had adequate allocation concealment, none of the trials blinded patients or caregivers, and only two trials blinded data collectors and outcome assessors. Five of the 10 trials were stopped prematurely before reaching their planned sample size: one each for futility,16 futility and harm,13 shortage of funding,14 slow enrollment,3 and harm.21 Both studies that cited harm as a reason to stop early reported excess strokes in the patients that received endovascular procedures.1,3,21

**Meta-analysis.** At 30 days and compared with CEA, CAS was associated with a nonsignificant reduction in the risk of death in five studies (RR, 0.61; 95% CI, 0.27-1.37; I² = 0%; Fig 2); a nonsignificant reduction in the risk of nonfatal MI in 3 studies (RR, 0.43; 95% CI, 0.17-1.11; I² = 0%; Fig 3); and a nonsignificant increase in the risk of any stroke in 5 studies (RR, 1.29; 95% CI, 0.73-2.26; I² = 40%; Fig 4). When only major and disabling strokes were included in the analysis, a similar nonsignificant increase in the risk of stroke was noted in patients who received CAS in 4 studies (RR, 1.06; 95% CI, 0.32-3.52; I² = 45%). When only Q-wave MIs were included in analysis, data were very limited and precluded meaningful analysis (1 Q-wave MI in the CAS group vs 4 in the CEA group). These results came from only two trials,13,15 because the other trials did not differentiate between Q and non-Q wave MI.

At 1 year and compared with CEA, CAS was associated with a nonsignificant reduction in the risk of death in two studies (RR, 0.56; 95% CI 0.29-1.08) and a nonsignificant increase in the risks of stroke in two studies (RR, 1.35; 95% CI, 0.31-5.82).

**Equivalence analyses.** Fig 5 describes 30-day equiva-

2% to 3%.13,15 Thus, we explored equivalence thresholds between 2% and 3% on either side of no difference (RD, 0), creating a region of equivalence (eg, from −3% to +3% RD) for each outcome. To claim equivalence, the entire confidence interval around the RD for an outcome should reside within the region of equivalence.

**RESULTS**

**Study identification.** Fig 1 depicts the yield of our search and selection procedures: of 498 potentially eligible references, 10 proved eligible.13-22 Table I summarizes their characteristics. These RCTs enrolled 3182 participants (mean size, 318 patients) who were a mean age of 68 years. In the 10 selected trials, the angioplasty procedures included stenting, and in all selected trials published since 2004, the angioplasty procedures included the use of cerebral protection devices. The follow-up period ranged from 1 to 45 months, with most studies reporting 30-day out-

**Table I.** Characteristics of included randomized trials

<table>
<thead>
<tr>
<th>Author ( year)</th>
<th>Trial name</th>
<th>Patients, No.</th>
<th>Use of stents (%)</th>
<th>Use of cerebral protective devices, %</th>
<th>Mean age of subjects, year</th>
<th>Symptoms</th>
<th>Operative risk</th>
<th>Follow-up, months</th>
<th>Degree of stenosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naylor (1998)</td>
<td>Leicester</td>
<td>23</td>
<td>100</td>
<td>0</td>
<td>67.2</td>
<td>Yes</td>
<td>Average</td>
<td>1</td>
<td>&gt;70</td>
</tr>
<tr>
<td>Alberts (2001)</td>
<td>Wallstent</td>
<td>219</td>
<td>100</td>
<td>0</td>
<td>68.3</td>
<td>Yes</td>
<td>NR</td>
<td>12</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Brooks (2001)</td>
<td>Kentucky</td>
<td>104</td>
<td>100</td>
<td>0</td>
<td>68.0</td>
<td>Yes</td>
<td>NR</td>
<td>48</td>
<td>&gt;70</td>
</tr>
<tr>
<td>CAVATAS (2001)</td>
<td>CAVATAS</td>
<td>504</td>
<td>26</td>
<td>0</td>
<td>67.0</td>
<td>Mixed</td>
<td>Average</td>
<td>36</td>
<td>NR</td>
</tr>
<tr>
<td>Brooks (2004)</td>
<td>Kentucky</td>
<td>85</td>
<td>100</td>
<td>0</td>
<td>68.2</td>
<td>No</td>
<td>NR</td>
<td>48</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Yadav (2004)</td>
<td>SAPPHIRE</td>
<td>334</td>
<td>100</td>
<td>95.6</td>
<td>72.6</td>
<td>Mixed</td>
<td>High</td>
<td>36</td>
<td>&gt;50; &gt;80</td>
</tr>
<tr>
<td>Mas (2006)</td>
<td>EVA-3S</td>
<td>527</td>
<td>100</td>
<td>91.90</td>
<td>69.7</td>
<td>Yes</td>
<td>Average</td>
<td>6</td>
<td>&gt;60</td>
</tr>
<tr>
<td>The Space Group (2006)</td>
<td>SPACE</td>
<td>1200</td>
<td>100</td>
<td>NR (mixed)</td>
<td>67.9</td>
<td>Yes</td>
<td>Average</td>
<td>1</td>
<td>&gt;70</td>
</tr>
<tr>
<td>Ling (2006)</td>
<td>TESCAS-C</td>
<td>166</td>
<td>100</td>
<td>100</td>
<td>63</td>
<td>Mixed</td>
<td>NR</td>
<td>6</td>
<td>&gt;50; &gt;70</td>
</tr>
<tr>
<td>Hoffman (2006)</td>
<td>BACASS</td>
<td>20</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>45</td>
<td>&gt;70</td>
</tr>
</tbody>
</table>

*BACASS, Basle carotid artery stenting study; CAVATAS, Carotid and Vertebral Artery Transluminal Angioplasty Study; ETA-3S, Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis; NR, not reported; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SPACE, Stent-Protected Percutaneous Angioplasty Versus Carotid Endarterectomy; TESCAS-C, Treatment of Carotid Arteriosclerotic Stenosis in China.

*Stenosis in symptomatic patients was >50% and in asymptomatic patients was >80%.

*Stenosis in symptomatic patients was >50% and in asymptomatic patients was >70%.
MI using an equivalence zone of 2%. However, the effects on stroke would only be considered equivalent if an equivalence zone of 3% is used. We consider this to be an unacceptably wide zone of equivalence that could mask an important benefit of CEA over CAS.

Subgroup and sensitivity analysis. Table III describes the results of our planned subgroup analyses. We found no significant treatment–subgroup interaction for subgroups on the basis of patient symptoms, the use of protective devices, and stopping trials prematurely. We found insufficient data to conduct the other planned subgroup analyses. Within-trial subgroup analyses, that is, the analyses presented in the original articles and not the ones conducted across trials, failed to identify significant treatment interactions based on the severity of stenosis, patient age and gender, the presence of symptoms, or whether MI was associated with Q wave. These latter analyses were reported in the individual trials, and we found insufficient data to conduct them between trials.

The inclusion of CAVATAS and Leicester does not change the conclusions of this review regarding death (RR, 0.85; 95% CI, 0.43–1.66; I² = 0%) and stroke (RR, 1.25; 95% CI, 0.77–2.02; I² = 42%). The MI outcome, however, becomes statistically significant, with a lower incidence of MI with CAS (RR, 0.39; 95% CI, 0.16–0.96; I² = 0%). The clinical significance of this finding is unknown considering that this was a mix of Q and non-Q wave MIs.

We compared three other statistical methods for continuity correction to allow the inclusion of studies with sparse data. The pooled estimates for death, stroke, and MI were not significantly affected by the choice of method. Similarly, the inclusion of trials with zero total events did not significantly affect RRs of the three outcomes to the extent that RRs continued to be imprecise and crossed the line of no effect (RR, 1.0).

Lastly, we repeated analysis by using the fixed-effect model to ascertain the magnitude of the effect of heterogeneity on results (both models are shown in Figs 2, 3, and
4). The RR of death and MI did not change because of low heterogeneity (ie, $I^2 = 0\%$); however, the outcome of any stroke became more precise and its CI became narrower under the fixed-effect model.

DISCUSSION

Our findings. We conducted a systematic review and meta-analyses of RCTs comparing CAS and CEA for carotid stenosis. We found 10 trials that provided low to moderate quality evidence given that they poorly reported or implemented bias protection measures. Although blinding of patients and surgeons is often not feasible in surgical trials, blinding of data collectors and outcome assessors, and allocation concealment are possible. In addition, half of the trials were stopped early and yielded imprecise results on the outcome of stroke, which is the main outcome these two procedures are primarily intended to prevent. Both procedures appear equivalent on their effects on death and nonfatal MI; the difference in risk of strokes between procedures remains inconclusive, with a trend toward superiority favoring CEA. This trend is likely clinically important considering that patients seek these procedures exclusively to prevent stroke and because more of the CI of the risk difference lies in the region consistent with increased risk of stroke. Limited data were available for subgroup analyses, which appeared to have wide CI and were underpowered.

Limitations and strengths of this review. Several limitations weaken the inferences we can draw in this review. The primary evidence is of low to moderate quality due to the methodologic features of primary studies and the imprecise results. Reporting bias may affect the results of this review because one trial reported only composite outcomes and did not contribute to the pooled estimates of individual outcomes, and two trials were unpublished and were only available as abstracts. In addition, five of these 10 trials were halted before reaching their planned sample size, citing reasons of futility, shortage of enrollment, or harm. Stopping RCTs prematurely for futility produces imprecise results that, as is the case of the outcome of stroke in the present review, cannot be made precise enough even after pooling, thus reducing the scientific and societal value of this research.

Applicability of our results may be limited because some trials selected participant clinicians and centers on the...
Table III. Subgroup analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR (95% CI)</th>
<th>Interaction test (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI at 30 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No use of cerebral protection device</td>
<td>1.42 (0.46-4.42)</td>
<td>.46</td>
</tr>
<tr>
<td>Using cerebral protection device</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials stopped early</td>
<td>0.64 (0.28-1.48)</td>
<td>.32</td>
</tr>
<tr>
<td>Trials not stopped early</td>
<td>1.35 (0.46-3.97)</td>
<td>.86</td>
</tr>
<tr>
<td>Symptomatic patients</td>
<td>0.73 (0.28-1.93)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic patients</td>
<td>0.95 (0.06-16.36)</td>
<td></td>
</tr>
<tr>
<td>Stroke at 30 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No use of cerebral protection device</td>
<td>2.27 (0.16-31.46)</td>
<td>.92</td>
</tr>
<tr>
<td>Using cerebral protection device</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials stopped early</td>
<td>2.24 (0.96-5.20)</td>
<td>.12</td>
</tr>
<tr>
<td>Trials not stopped early</td>
<td>1.10 (0.76-1.60)</td>
<td>.60</td>
</tr>
<tr>
<td>Symptomatic patients</td>
<td>2.08 (0.88-4.90)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic patients</td>
<td>0.95 (0.06-16.36)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI at 30 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No use of cerebral protection device</td>
<td>0.19 (0.002-15.75)</td>
<td>.72</td>
</tr>
<tr>
<td>Using cerebral protection device</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials stopped early</td>
<td>0.43 (0.17-1.11)</td>
<td></td>
</tr>
<tr>
<td>Trials not stopped early</td>
<td>0.42 (0.15-1.16)</td>
<td>.92</td>
</tr>
<tr>
<td>Symptomatic patients</td>
<td>0.72 (0.14-3.72)</td>
<td>.87</td>
</tr>
<tr>
<td>Asymptomatic patients</td>
<td>0.95 (0.06-16.36)</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, relative risk.

*aSubgroup analysis is conducted by calculating treatment effect from studies with a particular trait (eg, studies in which protection devices were used) and from studies without the trait (eg, studies in which protection devices were not used).

*bRandom-effect values >1.00 favor endarterectomy.

*cOnly one study with zero events contributed to the pooled estimate of asymptomatic patients.

basis of their surgical volume, outcomes, and operator experience and learning curve. Although most trials described these attributes, none of them had enough power to adjust their analysis accordingly.

It is also important to recognize that equivalence analysis is based on the risk difference and is highly dependent on the control event rates (CEA event rates) in different practice settings. For example, in a setting that deals with patients with multiple comorbidities and a known higher risk for preoperative death and MIs, CEA and CAS may not be equivalent in these two outcomes.

Our use of state-of-the-art systematic search, data collection, and summary methods, author contact to limit reporting bias, explicit quality assessment, and parsimonious analyses represent the strengths of this work.

Comparison with previous reviews. Compared with reviews done 5 years ago, our RR estimates are similar despite pooling data from 1933 additional randomized patients. Our results differ, however, from the results of recent reviews. Compared with Ederle et al, our analysis of the individual outcomes of death, stroke, and nonfatal MI included one additional trial. Compared with Brahmandam et al and Ringleb et al, our review included two additional trials. Our random-effects meta-analyses yielded estimates with less precision (wider CIs) than the fixed-effects meta-analyses used in the latter two reviews. We planned and executed a random-effects approach given the undeniable inconsistency in patients, interventions, and outcomes across the eligible trials that makes neglect of these between-study differences—the key assumption in the fixed-effects approach—unsatisfactory. To our knowledge, the present review is the first to explore equivalence using absolute risk measures. These analyses determined the extent to which the two procedures are equivalent in reducing the risk of death and nonfatal MI; however, limited precision made it impossible to draw similar inferences about their effect on the risk of stroke.

Implications for further research. The investigators of ongoing trials (Carotid Revascularization Endarterectomy vs. Stent Trial, International Carotid Stenting Study, Carotid Stenting vs Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients-1, Asymptomatic Carotid Surgery Trial-2, Transatlantic Asymptomatic Carotid Intervention Trial, Agostoni et al, and Link et al) should consider continuing patient recruitment until they reach the planned sample size of the trial. If concerns about patient safety arise, we encourage investigators to use rigorous statistical methods for stopping early and make interim data assessments “early looks at the data” infrequent and as delayed as possible in the course of a trial. Otherwise, these trials may produce similarly imprecise results and leave patients and clinicians with significant ambiguity about the best treatment option for carotid stenosis. Indeed, it is plausible that these two procedures are effective but may offer distinct advantages in different patient groups; for example, patients with complex carotid anatomy, patients with tenuous cardiovascular health, and centers with differential expertise for each of these procedures. Subgroup inferences will require, however, the conduct of large RCTs with inclusion criteria that permit high-risk patients to enter the trials.

CONCLUSION

Evidence of moderate quality is inconclusive in establishing superiority, noninferiority, or equivalence of stenting vs endarterectomy of the carotid arteries in patients with carotid stenosis at risk of stroke. Both procedures seem equivalent in terms of death and nonfatal MI, but the effect on stroke prevention remains unclear.

This article is dedicated to the memory of Dr Robert W. Hobson II in honor of all his contributions to our understanding of the management of carotid disease.

AUTHOR CONTRIBUTIONS

Conception and design: MM, VM, DF, ME, GG, RH, PE
Analysis and interpretation: MM, VM, GG
Data collection: MM, DF, ME
Writing the article: MM, VM, DF, ME, GG, RH, PE
Critical revision of the article: MM, VM, DF, ME, GG, RH,* PE
Final approval of the article: MM, VM, DF, ME, GG, PE
Statistical analysis: MM, VM, GG
Obtained funding: VM, RH
Overall responsibility: MM

*Dr Hobson died before he could approve the revisions; however, he did approve the final version that was initially submitted to the Journal of Vascular Surgery (before revisions).

REFERENCES

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