PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The efficacy and safety of bevacizumab plus erlotinib versus bevacizumab or erlotinib alone in the treatment of non-small-cell lung cancer: a systematic review and meta-analysis
AUTHORS	Zhang, Shu; Mao, Xiao-dong; Wang, Hai-tao; Cai, Feng; Xu, Jing

VERSION 1 - REVIEW

REVIEWER	SW Duffy Queen Mary University of London, UK
REVIEW RETURNED	24-Mar-2016

GENERAL COMMENTS	1. This paper reviews trials of bevacizumab and erlotinib in combination against one or other single agent in non-small cell lung cancer. The first question which arises is whether the control groups are homogeneous. That Is, is it reasonable to expect the combination to have the same differential effect over bevacizumab alone as over erlotinib alone? 2. Remind the reader how overall response rate is derived, please. 3. Statistical methods: although it is common practice to use a random effects model in response to observed heterogeneity, this does not really solve the problem. It is important to identify the reasons for heterogeneity. The authors do partly address this, in finding no hetereogeneity when one study (reference 16) is excluded. The results of this study are clearly in conflict with those of the others but it is worth exploring whether there are design or treatment features which are peculiar to this trial, and which might explain the atypical result? 4. The discussion could be shortened without serious loss to the paper's message.

REVIEWER	Isabel Allen University of California, San Francisco USA
REVIEW RETURNED	19-Apr-2016

GENERAL COMMENTS	A well done meta-analysis - it uses the Jadad Quality Scoring method with is no longer recommended by Cochrane and others. I would recommend reviewing the chapter on risk of bias in the Cochrane Handbook & redoing the quality assessment. (see Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration. 2009. Available from www.cochrane-handbook.org) I would also recommend that the authors register their meta-analysis

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	with Prospero: http://www.crd.york.ac.uk/PROSPERO/

REVIEWER	Valentina Assi University of Edinburgh, UK
REVIEW RETURNED	02-May-2016

GENERAL COMMENTS	Zhang and colleagues presented a systematic review and meta-analysis on the potential benefits of a therapy that combines bevacizuman and erlotinib for treating patients with non-small-cell lung cancer, rather than treating them with only one of these two therapies. The study is uptodate, and provides valid evidence to help decision-makers when treating this condition. However the review has several limitations and could benefit from some corrections. Introduction: - One paragraph of the introduction is dedicated to crizotinib, however it is quite unclear the reason for this, as it does no seem relevant to the rest of the review, and crizotinib is no longer mentioned. Possibly the authors could clarify why they felt the need for introducing this alternative treatment, its role in their rationale for this study. Or simply cut it out. - The aim of this study was to assess the efficacy and safety of bevacizumab plus erlotinib in the first- or second-line of treatment of patients with NSCLC. However the introduction does not clearly explain the importance of focusing on the line of treatment, the authors could expand on that. - It is confusing to say that Herbst RS [15] is placebo-controlled, as in this study the control arm is treated with erlotinib alone, not with placebo. Methods: - One of the aims of the current study is to investigate the efficacy of the combination treatment. The authors could introduce more clearly the outcomes of interest selected to describe such efficacy. - When assessing the quality of the studies, one may consider as well their statistical power. Under-recruitment could be a red-flag too. - The approach to pool the estimates should be used across all the analyses consistently. One should not have a mix of random-effects and fixed-effect analyses within the same systematic review. Also it is advisable not to base the choice of random-effects or fixed-effect on the heterogeneity test, as this is often underpowered. It would be better to decide the approach to use at a protocol stage, i.e. before even running the search. . The current meta-analysis pools together results from studies comparing the combination treatment to bevacizumb or erlotinib alone. These implies that the control arms received different treatments and thus that the meta-analysis might be unbalanced. It would be interesting to investigate whether the combination treatment appeared more effective when compared to erlotinib or to

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	bevacizumab alone. The authors could comment on this in the text, both in the methods and in the results section. - Given the aim of this review, it sounds very sensible to conduct subgroup analysis according to the line of treatment. It would be beneficial to the readers, though, if the authors could explain this choice. What kind of differences are the auhors expecting? Results: - "Identification of eligible studies": the wording in this section is overall fairly confusing. For instance, it seems like 42 studies were excluded and THEN the 57 remaining studies were selected for full-text review, i.e. there would be 42 extra studies. My suggestion would be to reword this whole section so that it describes more clearly the selection process, also displayed in figure 1. - "Characteristics of eligible studies and quality assessment": When describing the quality of the eligible studies, the authors could comment a bit more on the results from table 2. For instance it appears that the main issue in these studies is related to drop-out and withdrawals. As missing data are a serious threat of bias for a study and a meta-analysis, the authors may want to comment on this and on the extent of this problem (i.e. what was the average missing rate?) -In the Methods section the authors stated that they would explore the treatment effects in subpopulations of patients defined by demographics and baseline characteristics. This analysis was only performed for PFS, though. I would recommend the authors to perform this subpopulation analysis for all the outcomes of interest, or explain their reasons for focusing only on PFS. In the latter case it would be advisable to modify the text of the statistical analysis section. -"Progression free survival": Results from Ciuleanu's study were substantially different from the other four. I would encourage the authors to try to describe the practical reasons of such difference (e.g. follow-up, population, structure of the intervention...). This would help justifying excluding it from the analysis as source of potenial heterogeneity. Also at the end of this section it is not very clear that Ciuleanu was included in the analysis again. - "Adverse events": Table 3 should have more details. It is not clear how these RRs were computed and the number of studies and patients included for each adverse events of interest. Especially in this case, it would be interesting to know the results stratified by control-treatment group. Discussion -Discussion would have to be partially amended if the suggested changes were to be accepted. For instance it should include a comment on the potential differences in the results according to the control-treatment group. -There are a few typos or missing spaces in the text. Nothing some proof-reading cannot fix.

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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: SW Duffy
Institution and Country: Queen Mary University of London, UK
Competing Interests: None declared.

1. This paper reviews trials of bevacizumab and erlotinib in combination against one or other single agent in non-small cell lung cancer. The first question which arises is whether the control groups are homogeneous. That Is, is it reasonable to expect the combination to have the same differential effect over bevacizumab alone as over erlotinib alone?
Response: Thanks for insightful comments. We agree with you that since there was heterogeneity among the control groups, the combination therapy would have different treatment effects when it was compared with different controls. Therefore, we conducted subgroup analysis based on the comparators. The subgroup analysis showed that, combined therapy did not prolong OS compared with either bevacizumab (HR=0.94, 95%CI: 0.76–1.17; P=0.602) or erlotinib (HR=0.97, 95%CI: 0.80–1.18; P=0.770). Combination of bevacizumab with erlotinib significantly improved PFS compared with either bevacizumab (HR=0.60, 95%CI: 0.51–0.71; P<0.001) or erlotinib alone (HR=0.78, 95%CI: 0.65–0.93; P=0.006). Patients with NSCLC who were treated with combination therapy had similar ORRs as those treated with either bevacizumab (RR=1.43, 95% CI: 0.72–2.85; P=0.304) or erlotinib alone (RR=0.88, 95% CI: 0.44–1.75; P=0.713). We have added these sentences in the Results Part in the revised manuscript.

2. Remind the reader how overall response rate is derived, please.
Response: Thanks for your good comments. The overall response rate is calculated from the summary of complete response and partial response. Accordingly, we have added this sentence in the revised manuscript. Please see line 16, page 6.
3. Statistical methods: although it is common practice to use a random effects model in response to observed heterogeneity, this does not really solve the problem. It is important to identify the reasons for heterogeneity. The authors do partly address this, in finding no hetereogeneity when one study (reference 16) is excluded. The results of this study are clearly in conflict with those of the others but it is worth exploring whether there are design or treatment features which are peculiar to this trial, and which might explain the atypical result?
Response: Thanks for your valuable comments. The ref 16 was a phase 2, open-label, multicenter, randomized trials, with the objectives to evaluate the efficacy and safety of bevacizumab in combination with either erlotinib or chemotherapy in advanced NSCLC. This study enrolled 124 patients (bevacizumab plus erlotinib (BE), 63; bevacizumab plus chemotherapy (BC), 61), but all of these patients had withdrawn from trial treatment by the time of the final analysis. Thus, the results were calculated from the updated interim analysis, which demonstrated that BE regimen had a shorter PFS and a higher incidence of death than BC. This resulted in contrary results with the other four studies. Moreover, the small valid sample size might also account for the potential heterogeneity between this and the other four studies.
Actually, we have presented a detailed description about this study in the paragraph 3 of Discussion Part.

4. The discussion could be shortened without serious loss to the paper's message.
Response: Thank you for your good suggestions. Accordingly, we have deleted several sentences in the discussion part.

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Reviewer: 2
Reviewer Name: Isabel Allen
Institution and Country: University of California, San Francisco, USA
Competing Interests: None

A well done meta-analysis - it uses the Jadad Quality Scoring method with is no longer recommended by Cochrane and others. I would recommend reviewing the chapter on risk of bias in the Cochrane Handbook & redoing the quality assessment. (see Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration. 2009. Available from www.cochrane-handbook.org)
Response: Thanks very much for your insightful and valuable comments. Accordingly, we have assessed the risk of bias in included RCTs with the method recommended by the Cochrane Collaboration. The quality of evidence for the outcome measures was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The details of the risk-of-bias assessment are presented in Figure 2.

I would also recommend that the authors register their meta-analysis with Prospero: http://www.crd.york.ac.uk/PROSPERO/
Response: Thanks very much for your good suggestion. We are now doing the work of registering this meta-analysis with Prospero.

Reviewer: 3
Reviewer Name: Valentina Assi
Institution and Country: University of Edinburgh, UK
Competing Interests: None declared

Zhang and colleagues presented a systematic review and meta-analysis on the potential benefits of a therapy that combines bevacizuman and erlotinib for treating patients with non-small-cell lung cancer, rather than treating them with only one of these two therapies. The study is up to date, and provides valid evidence to help decision-makers when treating this condition.
However the review has several limitations and could benefit from some corrections.

Introduction:

- One paragraph of the introduction is dedicated to crizotinib, however it is quite unclear the reason for this, as it does not seem relevant to the rest of the review, and crizotinib is no longer mentioned. Possibly the authors could clarify why they felt the need for introducing this alternative treatment, its role in their rationale for this study. Or simply cut it out.
Response: Thanks for your good comment. We agree with you that the introduction of crizotinib is un-relevant to our topic. Therefore, we have deleted this paragraph in the revised manuscript.

- The aim of this study was to assess the efficacy and safety of bevacizumab plus erlotinib in the first- or second-line of treatment of patients with NSCLC. However the introduction does not clearly explain the importance of focusing on the line of treatment, the authors could expand on that.
Response: Thanks very much for your insightful comments. Since the treatment-line might affect the efficacy of bevacizumab and erlotinib, we conduct the subgroup analysis based on line of treatment. Bevacizumab and erlotinib would result in different treatment outcomes when they were used in

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different line of treatment. This has been reported in the Introduction Part. In the ref 6, bevacizumab combined with paclitaxel and carboplatin as first-line in the treatment of NSCLC. And it showed beneficial effects in PFS and OS. However, in the ref 7, which examined bevacizumab plus cisplatin and gemcitabine in the first-line treatment of NSCLC, the regimen did not produce benefit in OS. With regard to erlotinib, when it was used in combination with second- or third-line monotherapy, it improved the OS (ref 9). Therefore, we were wondering whether the combined treatment would result in different clinical outcomes when they were used in different line-treatment. That's why we conducted subgroup analysis according to the line of treatment.
To give a clearly explain for this issue, we have added a few sentences in the Introduction Part in the revised manuscript.

- It is confusing to say that Herbst RS [15] is placebo-controlled, as in this study the control arm is treated with erlotinib alone, not with placebo.
Response: Thanks very much for your valuable comments. We agree with you that, in the trial conducted by Herst RS [15], patients in the control group were treated with erlotinib, not with placebo. However, in this study, we described it as "a double-blind, placebo-controlled, phase 3 trial". Actually, this description was cited from the original study in the Title (Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): a double-blind, placebo-controlled, phase 3 trial) and Methods Part (In our double-blind, placebo-controlled, randomised phase 3 trial).
Moreover, we mentioned erlotinib rather than placebo as the control arm in the sentence (In a double-blind, placebo-controlled, phase 3 trial, this combination regimen significantly prolonged PFS in patients with recurrent or refractory NSCLC compared with the effects of erlotinib alone). We hope this would not confuse the readers.

Methods:

- One of the aims of the current study is to investigate the efficacy of the combination treatment. The authors could introduce more clearly the outcomes of interest selected to describe such efficacy.
Response: Thanks for your insightful comments. We think it is very useful to give a more clearly introduction of the efficacy outcomes. And we described the efficacy outcomes of each study in the Discussion Part. Please see paragraph 2-4 of the Discussion Part.

- When assessing the quality of the studies, one may consider as well their statistical power. Under-recruitment could be a red-flag too.
Response: Many thanks for your insightful comments. We used the Jadad scale to assess the quality of studies, which consisted three items to describe the RCT, including randomization, masking, and dropouts and withdrawals. Because the statistical power is not regard as an important factor for the quality assessment, we could not consider it during the assessment process. But we still appreciate your valuable suggestion.

- The approach to pool the estimates should be used across all the analyses consistently. One should not have a mix of random-effects and fixed-effect analyses within the same systematic review. Also it is advisable not to base the choice of random-effects or fixed-effect on the heterogeneity test, as this is often underpowered. It would be better to decide the approach to use at a protocol stage, i.e. before even running the search.
Response: Thanks very much for your valuable comments. In this meta-analysis, we used a fixed-effects model or random-effects model to pool the estimates according to the heterogeneity among the individual studies. When significant heterogeneity was found, a random-effects model was used; otherwise, a fixed-effects model was used.
According to the Cochrane Library, when statistical heterogeneity is identified among a group of trials, a number of options are available to be considered suitable for a meta-analysis. Among these

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options, performing a random effects rather than a fixed effects meta-analysis is one of the options to incorporate heterogeneity among trials. The reasons could be explained as followings: in a heterogeneous set of studies, a random-effects meta-analysis will award relatively more weight to smaller studies than such studies would receive in a fixed effect meta-analysis. This is because small studies are more informative for learning about the distribution of effects across studies than for learning about an assumed common treatment effect [Cochrane Library 4.2.2: 8.7.4 Incorporating heterogeneity into random effects models].
Moreover, several published meta-analysis also used a fixed-effects or random-effects model to pool the estimates according to the heterogeneity [Assessment of the potential diagnostic value of serum p53 antibody for cancer: a meta-analysis. Plos One 2014; 9(6): e999255; Systematic review and meta-analysis of tumor biomarkers in predicting prognosis in esophageal cancer. BMC Cancer, 2013;13:539].

The current meta-analysis pools together results from studies comparing the combination treatment to bevacizumb or erlotinib alone. These implies that the control arms received different treatments and thus that the meta-analysis might be unbalanced. It would be interesting to investigate whether the combination treatment appeared more effective when compared to erlotinib or to bevacizumab alone. The authors could comment on this in the text, both in the methods and in the results section.
Response: Thanks very much for your valuable suggestions. Accordingly, we have conducted a subgroup analysis based on the comparators to investigate whether the combination treatment would be more effective than erlotinib or bevacizumab alone. These results were presented in the revised manuscript [second paragraph in Overall Survival Part, second paragraph in Progression Free Survival Part; first paragraph in Overall Response Rate].
- Given the aim of this review, it sounds very sensible to conduct subgroup analysis according to the line of treatment. It would be beneficial to the readers, though, if the authors could explain this choice. What kind of differences are the authors expecting?
Response: Thanks for your insightful comments. Since the treatment-line might affect the efficacy of bevacizumab and erlotinib, we conduct the subgroup analysis based on line of treatment. Bevacizumab and erlotinib would result in different treatment outcomes when they were used in different line of treatment. And this has been presented in the Introduction Part. In the ref 6, bevacizumab combined with paclitaxel and carboplatin as first-line in the treatment of NSCLC. And it showed beneficial effects in PFS and OS. However, in the ref 7, which examined bevacizumab plus cisplatin and gemcitabine in the first-line treatment of NSCLC, the regimen did not produce benefit in OS. With regard to erlotinib, when it was used in combination with second- or third-line monotherapy, it improved the OS (ref 9). Therefore, we were wondering whether the combined treatment would result in different clinical outcomes when they were used in different line-treatment. That's why we conducted subgroup analysis according to the line of treatment.

Results:

- "Identification of eligible studies": the wording in this section is overall fairly confusing. For instance, it seems like 42 studies were excluded and THEN the 57 remaining studies were selected for full-text review, i.e. there would be 42 extra studies. My suggestion would be to reword this whole section so that it describes more clearly the selection process, also displayed in figure 1.
Response: Thanks very much for your good comments. Accordingly, we have changed the sentence "Of these, 438 studies were removed as duplicate records, and 228 and 42 studies were excluded after a review of the title/abstract and full-text information, respectively (Figure 1)" with "Of these, 438 studies were removed as duplicate records, and 228 studies were excluded after a review of the title/abstract (Figure 1)" in the revised manuscript.

- "Characteristics of eligible studies and quality assessment": When describing the quality of the eligible studies, the authors could comment a bit more on the results from table 2. For instance it

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appears that the main issue in these studies is related to drop-out and withdrawals. As missing data are a serious threat of bias for a study and a meta-analysis, the authors may want to comment on this and on the extent of this problem (i.e. what was the average missing rate?)
Response: Many thanks for your constructive suggestions. In the assessing the quality of the included studies, all reported the method to generate the sequence of randomization, two used double-blind methods, and two reported the number and the reasons for withdrawal in each group.
Among the two studies provided the information about withdraw and dropouts, one reported that 8 of 61 (13.1%) patients in bevacizumab group and 6 of 63 (9.5%) patients in combination group withdrawn from trial treatment for safety reasons. Whereas, in another trial, the withdraw rate in the combination group and bevacizumab group were 13% and 28%, respectively.

-In the Methods section the authors stated that they would explore the treatment effects in subpopulations of patients defined by demographics and baseline characteristics. This analysis was only performed for PFS, though. I would recommend the authors to perform this subpopulation analysis for all the outcomes of interest, or explain their reasons for focusing only on PFS. In the latter case it would be advisable to modify the text of the statistical analysis section.
Response: Thanks for your constructive and valuable suggestions. Actually, in the data analysis, we have tried to conducted subgroup analysis based on the demographics and baseline characteristics. However, only the PFS data in subpopulations was provided by these included studies. Thus, we could not perform the subgroup analysis in OS and ORR.
-"Progression free survival": Results from Ciuleanu's study were substantially different from the other four. I would encourage the authors to try to describe the practical reasons of such difference (e.g. follow-up, population, structure of the intervention...). This would help justifying excluding it from the analysis as source of potential heterogeneity. Also at the end of this section it is not very clear that Ciuleanu was included in the analysis again.
Response: Thanks very much for your insightful and valuable comments. The trial conducted by Ciuleanu was a phase 2, open-label, multicenter, randomized trials, with the objectives to evaluate the efficacy and safety of bevacizumab in combination with either erlotinib or chemotherapy in advanced NSCLC. This study enrolled 124 patients (bevacizumab plus erlotinib (BE), 63; bevacizumab plus chemotherapy (BC), 61), but all of these patients had withdrawn from trial treatment by the time of the final analysis. Thus, the results were calculated from the updated interim analysis, which demonstrated that BE regimen had a shorter PFS and a higher incidence of death than BC. This resulted in contrary results with the other four studies. Moreover, the small valid sample size might also account for the potential heterogeneity between this and the other four studies. Actually, we have presented a detailed description of this study in the paragraph 3 of Discussion Part.

- "Adverse events": Table 3 should have more details. It is not clear how these RRs were computed and the number of studies and patients included for each adverse events of interest. Especially in this case, it would be interesting to know the results stratified by control-treatment group.
Response: Thanks for your good comment. All the included studies reported the adverse events in Table 3. Accordingly, we have added the number of the patients in combination and monotherapy group in the revised Table 3.

Discussion

-Discussion would have to be partially amended if the suggested changes were to be accepted. For instance it should include a comment on the potential differences in the results according to the control-treatment group.
Response: Thanks very much for your insightful suggestions. According to your suggestion, we have conducted subgroup analysis based on the control-treatment group. However, the subgroup results were consistent with the overall results, and no new results were observed. Then we presented the subgroup results in the Results Part and comments in the Discussion Part (line 24, page10)

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-There are a few typos or missing spaces in the text. Nothing some proof-reading cannot fix.
Response: Thank you for your good comments. We have revised the whole manuscript with the assistance from a native English speaker. Now we hope the revised paper will provide a more readable description on the method and the main results of this study.

VERSION 2 – REVIEW

REVIEWER	Valentina Assi University of Edinburgh, UK
REVIEW RETURNED	18-May-2016

GENERAL COMMENTS	Further comments: - "placebo-controlled" referred to Herbst RS [15] is probably not necessary and actually a bit confusing. It could be just left out. - Description of the outcomes of interest: The authors were interested in the efficacy, but then failed to expand on what outcomes were selected to explain such efficacy and thus to describe them in further detail. Such description does not belong to the Discussion but to the Methods section as it would help understanding the search and extraction process followed by the authors to retrieve the data used in this review. - Approach for pooling data: The authors decided to discard my previous comment, but I do still feel that the analyses would be better using consistently the random-effects model. This approach is less conservative and takes into account the heterogeneity among the studies. As a matter of fact, the studies included in this review appear substantially diverse given the different control treatment, line of treatment, geographic region and so on.

VERSION 2 – AUTHOR RESPONSE

Further comments:

- "placebo-controlled" referred to Herbst RS [15] is probably not necessary and actually a bit confusing. It could be just left out.
Response: Thanks very much for your good comments. Accordingly, we have deleted the “placebo-controlled” in the revised manuscript. Please see line 18 page14.

- Description of the outcomes of interest: The authors were interested in the efficacy, but then failed to expand on what outcomes were selected to explain such efficacy and thus to describe them in further detail. Such description does not belong to the Discussion but to the Methods section as it would help understanding the search and extraction process followed by the authors to retrieve the data used in this review.
Response: Thanks for insightful comments. According to your suggestion, we have added the original data from each study into the methods section (line 8-13, page9; line 24-28, page 9; line 9-11, page 11). We hope that this could provide detailed information for the readers to understand the search and extraction process.

- Approach for pooling data: The authors decided to discard my previous comment, but I do still feel that the analyses would be better using consistently the random-effects model. This approach is less

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conservative and takes into account the heterogeneity among the studies. As a matter of fact, the studies included in this review appear substantially diverse given the different control treatment, line of treatment, geographic region and so on.

Response: Thanks for insightful and constructive comments. We found that the heterogeneity tests for all the outcomes except overall survival were significant, and data for overall survival was pooled using the fixed-effects model. Thus, we chose the random-effects model to re-analyze this outcome again. However, the pooled estimates did not change (Figure 3).

The re-edited Figure 3 is presented in the revised manuscript. At the bottom of this figure, it reads "note: weights are from random effects analysis", which indicates that random-effects model is used for this data analysis.

For the other three outcomes, because they were all pooled using random-effects model, we did not re-analyze them again.

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