

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Metoprolol for prophylaxis of postoperative atrial fibrillation in cardiac surgery patients: systematic review and meta-analysis
AUTHORS	Norhayati, Mohd Noor ; Shaiful Bahari, Ismail; Zaharah, Sulaiman; Nik Hazlina, Nik Hussain; Mohammad Aimanazrul, Zainuddin; Irfan, Muhammad

VERSION 1 – REVIEW

REVIEWER	Andrei M. Belyaev Auckland City Hospital, New Zealand
REVIEW RETURNED	10-Apr-2020

GENERAL COMMENTS	<ul style="list-style-type: none"> • Review of the manuscript "Metoprolol for prophylaxis of postoperative atrial fibrillation in cardiac surgery patients: systematic review and meta-analysis" • " written by Noor et al. and submitted to BMJOpen for consideration of publication. • My sincere comments to the authors: <ol style="list-style-type: none"> 1. Please, put "prolonged hospital stay" at the end of the sentence "The development of POAF...", after "myocardial infarction (Page 4, lines 52-54). 2. In the same sentence, change "myocardial infarctions" to "myocardial infarction" (Page 5, line 3). 3. Change " this figure" for more appropriate words (Page 5, line 3). 4. Change "The mechanism behind POAF" for "Aetiology of POAF" (Page 5, line 10). 5. Remove the sentence "POAF is usually asymptomatic, brief and paroxysmal" (Page 5, lines 16-18). This statement undermines the necessity for pharmacological prevention of postoperative atrial fibrillation. 6. Usually, the authors write the Introduction according to the following structure: A) Why is the problem important? B) What is known about the problem? C) Where is a knowledge gap or controversy? D) What can be done to eliminate this knowledge gap or controversy? E) What is the study hypothesis? F) What is the aim of the study? 7. In the Introduction, the authors should provide the reader with information on whether there are any meta-analyses on the evaluation of metoprolol for prophylaxis of POAF. 8. In the Eligibility Criteria, the authors mentioned that they considered RCT comparing metoprolol with a placebo or no treatment. However, the study aimed to compare metoprolol with other treatment options for prophylaxis against POAF (Page 5, line 47).
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	<p>9. There are no exclusion criteria for this study (Pages 5-6). Therefore, the reasons for the exclusion of 71 studies are unknown (Fig. 1).</p> <p>10. In Methods, the authors should define hypotension.</p> <p>11. The sentence "Three trials were compared against no treatment" is not clear (Results. Interventions. Page 9, line 33). Should be such RCTs excluded from the analysis?</p> <p>12. Remove "small" from the sentence "There was a small but significant reduction in POAF" (Page 11, line 18).</p> <p>13. What was p-value for the comparison of metoprolol versus no treatment or placebo in the development of POAF (Page 11, lines 18-20)?</p> <p>14. Figure 4 should present the results of the comparison of metoprolol versus placebo or no treatment, but it demonstrates the comparison against amiodarone.</p> <p>15. Remove "OR, Odds ratio" from tables 2-5, because relative risk (RR) was used in these tables to demonstrate the risk of AF.</p> <p>16. What are p-values for comparisons of metoprolol versus carvedilol, sotalol and amiodarone in the development of POAF, stroke, hypotension bradycardia and mortality (Pages 11-12)?</p> <p>17. Because carvedilol and metoprolol are both beta-blockers, it would be important to present the results of the analysis for different doses of carvedilol.</p>
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REVIEWER	Isabelle Greiss University of Montreal Hospital Center
REVIEW RETURNED	10-Apr-2020

GENERAL COMMENTS	<p>In the abstract, please state in conclusion that metoprolol was effective compared to placebo or no treatment and showed no difference with class III antiarrhythmics. Also, in results, please describe cardiovascular conditions included in the analysis to make conclusion easier to follow and adjust accordingly. In results, the nine trials are not compared to placebo or no treatment, but also with sotalol and amiodarone, please correct.</p> <p>In the Data extraction, please define what was the post operative period studied or the range of it.</p> <p>In Interventions, please state no treatment or placebo. Define same fashion for the drugs listed.</p> <p>In Outcomes, there is no mention of the two trials against amiodarone</p> <p>In Discussion, please check affirmation that metoprolol was superior to amiodarone (page 15, line 3), it is comparable from your findings. Also, it is of interest to elaborate why carvedilol would be superior to metoprolol. Ways of administration and timing to surgery should also be discussed, especially regarding metoprolol.</p> <p>In Conclusion, the aspect of rate of withdrawal is not mentioned in Results and should not be included.</p> <p>In table 1, name of compared drug missing for Ozaydin. Also "s" are missing for the words day. Please amend comparative drugs for Auer 2004, as this study is also listed for use of placebo</p> <p>In Table 2, please state placebo or non treatments</p> <p>In Figure 4 and supplemental, Figure 4 please state against placebo or no treatment</p>
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REVIEWER	Hiroshi Furukawa Department of Cardiovascular Surgery Tokyo Women's Medical University Medical Center East Japan
REVIEW RETURNED	22-Apr-2020

GENERAL COMMENTS	<p>Dear Author,</p> <p>Thank you for submitting manuscript titled "Metoprolol for prophylaxis of postoperative atrial fibrillation in cardiac surgery patients: systematic review and meta-analysis"</p> <p>I have read your successful clinical study with great interest. I have reviewed and corrected this manuscript with minor revisions as follows for further acceptance of BMJ Open.</p> <p>Thank you for your consideration. If you have any questions and problems, please feel free to ask me ASAP.</p> <p>Reviewer comments</p> <p>This manuscript is well written about the clinical efficacy of Metoprolol for postoperative Af, but still some points to correct for acceptance of journal. I have minor comments. Please encourage considering and resubmitting following these comments.</p> <p>Minor comments</p> <p>1) In this manuscript, there are difference between metoprolol and placebo, however, unfortunately, there was no difference when compared with sotalol or amiodarone. This point will be negative impact from the scientific point of view. Please explain and discuss in this the part of discussion.</p> <p>2) References: The style seems to be a right form, please check again the instruction for author.</p>
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REVIEWER	Kristen Tecson Baylor Heart and Vascular Institute, USA
REVIEW RETURNED	13-May-2020

GENERAL COMMENTS	<p>Manuscript ID: bmjopen-2020-038364</p> <p>Title: Metoprolol for prophylaxis of postoperative atrial fibrillation in cardiac surgery patients: systematic review and meta-analysis</p> <p>Summary: The authors performed a literature search to conduct a meta-analysis to determine the effect of metoprolol on postoperative atrial fibrillation (POAF). The authors conclude that metoprolol is effective in preventing POAF compared with placebo, but not to other treatments. Death and thromboembolism were associated with open heart surgery, but risks were mitigated with metoprolol.</p> <p>Statistical review: I believe the authors conducted their analyses appropriately and thoroughly, to their best ability. There are limitations to the paper due to limitations of available data; however, they are clearly presented by the authors. Some of those specific concerns are as follows: including both blinded and open label trials, active controls and placebos, IV and oral administration, 8 from Europe and 1 from South America, inconsistent monitoring times, and heterogeneity in certain analyses. I agree with their decision/inability to perform subgroup analyses due to a small number of available trials.</p>
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	Please add explicitly to the text (not just in the table) that the definition of POAF was not the same across trials (some require 1 minute, some 5 minutes, etc.).
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Andrei M. Belyaev

Institution and Country: Auckland City Hospital, New Zealand

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below.

Review of the manuscript "Metoprolol for prophylaxis of postoperative atrial fibrillation in cardiac surgery patients: systematic review and meta-analysis " written by Noor et al. and submitted to BMJ Open for consideration of publication.

My sincere comments to the authors:

1. Please, put "prolonged hospital stay" at the end of the sentence "The development of POAF...", after "myocardial infarction (Page 4, lines 52-54).

Response from authors: Changes done as suggested.

'The development of POAF is associated with increased risk of thrombotic events, such as stroke, thrombophlebitis, myocardial infarction and prolonged hospital stay.'

2. In the same sentence, change "myocardial infarctions" to "myocardial infarction" (Page 5, line 3).

Response from authors: Changes done as suggested.

'The development of POAF is associated with increased risk of thrombotic events, such as stroke, thrombophlebitis, myocardial infarction and prolonged hospital stay.'

3. Change " this figure" for more appropriate words (Page 5, line 3).

Response from authors: Changes done as suggested.

'It is estimated that this problem will continue to grow, given that the patient population undergoing cardiac surgery is ageing and the incidence of POAF is largely age dependent.'

4. Change "The mechanism behind POAF" for "Aetiology of POAF" (Page 5, line 10).

Response from authors: Changes done as suggested.

'The aetiology of POAF is multifactorial and contributed to by certain factors, such as systemic and local inflammation and oxidative stress, as well as electrolyte imbalance.'

5. Remove the sentence "POAF is usually asymptomatic, brief and paroxysmal" (Page 5, lines 16-18). This statement undermines the necessity for pharmacological prevention of postoperative atrial fibrillation.

Response from authors: The sentence is removed.

6. Usually, the authors write the Introduction according to the following structure: A) Why is the problem important? B) What is known about the problem? C) Where is a knowledge gap or controversy? D) What can be done to eliminate this knowledge gap or controversy? E) What is the study hypothesis? F) What is the aim of the study?

A) Why is the problem important?

Response from authors: The text is in the first paragraph, first sentence.

'Post-operative atrial fibrillation (POAF) is the most important type of secondary atrial fibrillation (AF), representing a new-onset AF in the immediate period after cardiac surgery. POAF is a potentially lethal and morbid complication after open heart surgery.'

B) What is known about the problem?

Response from authors: The text is in the second paragraph, second sentence.

'POAF can lead to morbidity and mortality in high-risk patients. The development of POAF is associated with increased risk of thrombotic events, such as stroke, thrombophlebitis, myocardial infarction and prolonged hospital stay.'

C) Where is a knowledge gap or controversy?

Response from authors: The text is in the third paragraph, third last sentence.

'There are no definitive preventive strategies for AF following heart surgery.'

D) What can be done to eliminate this knowledge gap or controversy?

Response from authors: The text is in the third paragraph, second last sentence.

'The aim of this review is to investigate metoprolol in comparison with a control for prophylaxis against POAF in order to reduce the occurrence of adverse events in the post-operative period such as death and cardioembolic events.'

E) What is the study hypothesis?

Response from authors: The text is in the third paragraph, last sentence.

'We hypothesized that metoprolol is effective for prophylaxis against POAF compared to other treatment options.'

F) What is the aim of the study?

Response from authors: The text is in the third paragraph, second last sentence.

'The aim of this review is to investigate metoprolol in comparison with a control for prophylaxis against POAF ...'

7. In the Introduction, the authors should provide the reader with information on whether there are any meta-analyses on the evaluation of metoprolol for prophylaxis of POAF.

Response from authors: The following statement was included.

'There were a few meta-analyses for the evaluation of metoprolol for prophylaxis of POAF; following which, new trials were included in this review.'

8. In the Eligibility Criteria, the authors mentioned that they considered RCT comparing metoprolol with a placebo or no treatment. However, the study aimed to compare metoprolol with other treatment options for prophylaxis against POAF (Page 5, line 47).

Response from authors: We have rephrased the aim of the study as below.

'The aim of this review is to investigate metoprolol in comparison with a control for prophylaxis against POAF ...'

9. There are no exclusion criteria for this study (Pages 5-6). Therefore, the reasons for the exclusion of 71 studies are unknown (Fig. 1).

Response from authors: We excluded patients not undergoing cardiac surgery, with prior or concomitant AF and publications not in English language. Kindly refer to the paragraph in the Eligibility criteria subheading as below.

'We considered for inclusion trials that included patients who underwent cardiac surgery (both revascularisation and valve surgery) without prior or concomitant AF. There were no restrictions on age or other comorbidities, such as hypertension and diabetes. We only considered publications that were published in the English language.'

We have added a statement regarding the 71 excluded studies under the Trial selection subheading as below.

'We screened 86 records, excluded 71 records that obviously did not fulfil the eligibility criteria based on the title and abstract and reviewed the full texts of 15 studies.'

10. In Methods, the authors should define hypotension.

Response from authors: We have added the statement 'hypotension as reported by the clinicians' in the text.

11. The sentence "Three trials were compared against no treatment" is not clear (Results. Interventions. Page 9, line 33). Should be such RCTs excluded from the analysis?

Response from authors: We have modified the statement as 'placebo (or no active treatment)'.

12. Remove "small" from the sentence "There was a small but significant reduction in POAF" (Page 11, line 18).

Response from authors: We have removed 'small' as suggested.

13. What was p-value for the comparison of metoprolol versus no treatment or placebo in the development of POAF (Page 11, lines 18-20)?

Response from authors: We have included the p-value in the text as below.

'(416 patients; RR = 0.46, 95% CI: 0.33 to 0.66; I^2 = 0%; RD = -0.19, 95% CI: -0.28 to -0.10; p-value <0.001)'

14. Figure 4 should present the results of the comparison of metoprolol versus placebo or no treatment, but it demonstrates the comparison against amiodarone.

Response from authors: Figure 4 was presenting the results of the comparison of metoprolol versus placebo. While, Supplementary Figure 2, 3, 6 demonstrated the comparison of metoprolol versus amiodarone.

15. Remove "OR, Odds ratio" from tables 2-5, because relative risk (RR) was used in these tables to demonstrate the risk of AF.

Response from authors: The "OR, Odds ratio" in the footnotes of Table 2-5 were removed.

16. What are p-values for comparisons of metoprolol versus carvedilol, sotalol and amiodarone in the development of POAF, stroke, hypotension bradycardia and mortality (Pages 11-12)?

Response from authors: The p-values for comparisons of metoprolol versus carvedilol, sotalol and amiodarone were added.

17. Because carvedilol and metoprolol are both beta-blockers, it would be important to present the results of the analysis for different doses of carvedilol.

Response from authors: For carvedilol, there were two trials using 25 mg, one trial using 13 mg and one trial using 50 mg. Therefore, subgroup analysis could be performed due to limited number of trials in each subgroup. A statement has been added in the result section to address this as below.

'We were unable to construct a subgroup analysis based on the dosage of carvedilol due to the limited number of trials.'

Reviewer: 2

Reviewer Name: Isabelle Greiss

Institution and Country: University of Montreal Hospital Center

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below.

In the abstract, please state in conclusion that metoprolol was effective compared to placebo or no treatment and showed no difference with class III antiarrhythmics. Also, in results, please describe cardiovascular conditions included in the analysis to make conclusion easier to follow and adjust accordingly. In results, the nine trials are not compared to placebo or no treatment, but also with sotalol and amiodarone, please correct.

Response from authors: Correction were made in the Abstract and Conclusion as suggested.

'Metoprolol is effective in preventing POAF compared with placebo and showed no difference with class III anti-arrhythmic drugs.'

The following changes were made in the Result section.

'We identified nine articles as meeting the review inclusion criteria...'

'Three trials were compared against placebo 20 21 24, four against carvedilol 6 22 23 25, two against amiodarone 18 19, and two against sotalol 20 24'

'The primary outcome, i.e., the occurrence of a first POAF was measured in all the trials. The secondary outcomes (stroke, hypotension, bradycardia and death) were only measured in four trials...'

In the Data extraction, please define what was the postoperative period studied or the range of it.

Response from authors: We have defined the primary outcome as to the number of patients having POAF during the post-operative period as diagnosed by a physician on electrocardiogram. The post-operative period was the period assessed as relevant to the clinicians. However, we have also included the range of post-operative period observed in the Result section.

'POAF was reported as the first occurrence of AF in the post-operative period; however, the period of monitoring was not consistent throughout the trials. It ranges from immediately after surgery until seven days post-operation or discharge from hospital.'

In Interventions, please state no treatment or placebo. Define same fashion for the drugs listed. In Outcomes, there is no mention of the two trials against amiodarone.

Response from authors: The corrections were made as suggested.

'Three trials were compared against placebo or no treatment...'

'Two trials involved comparisons with sotalol 20 24, two with amiodarone 18 19 and four with carvedilol 6 22 23 25.'

In Discussion, please check affirmation that metoprolol was superior to amiodarone (page 15, line 3), it is comparable from your findings. Also, it is of interest to elaborate why carvedilol would be superior to metoprolol. Ways of administration and timing to surgery should also be discussed, especially regarding metoprolol.

Response from authors: We have done the corrections and added the text as below.

'we found that metoprolol significantly reduced POAF after cardiac surgery compared with the placebo, but it was not superior to carvedilol, sotalol or amiodarone.'

'We tried to use subgroup analysis to assess the dosage, routes of administration and the time at which the treatment was initiated but there were limited number of trials to enable to do so.'

In Conclusion, the aspect of rate of withdrawal is not mentioned in Results and should not be included.

Response from authors: We have removed 'rate of withdrawal' from the text.

In table 1, name of compared drug missing for Ozaydin. Also "s" are missing for the words day. Please amend comparative drugs for Auer 2004, as this study is also listed for use of placebo.

Response from authors: We have done the corrections in Table 1 as indicated. Thank you.

In Table 2, please state placebo or non treatments

Response from authors: We have done the correction in Table 2 as indicated. Thank you.

In Figure 4 and supplemental, Figure 4 please state against placebo or no treatment.

Response from authors: We have done the corrections as indicated. Thank you.

Reviewer: 3

Reviewer Name: Hiroshi Furukawa

Institution and Country:

Department of Cardiovascular Surgery

Tokyo Women's Medical University Medical Center East

Japan

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below.

Dear Author,

Thank you for submitting manuscript titled "Metoprolol for prophylaxis of postoperative atrial fibrillation in cardiac surgery patients: systematic review and meta-analysis"

I have read your successful clinical study with great interest. I have reviewed and corrected this manuscript with minor revisions as follows for further acceptance of BMJ Open.

Thank you for your consideration. If you have any questions and problems, please feel free to ask me ASAP.

Response from authors: Thank you

Reviewer comments

This manuscript is well written about the clinical efficacy of Metoprolol for postoperative Af, but still some points to correct for acceptance of journal. I have minor comments. Please encourage considering and resubmitting following these comments.

Minor comments

1) In this manuscript, there are difference between metoprolol and placebo, however, unfortunately, there was no difference when compared with sotalol or amiodarone. This point will be negative impact from the scientific point of view. Please explain and discuss in this the part of discussion.

Response from authors: We have added the text as below.

'we found that metoprolol significantly reduced POAF after cardiac surgery compared with the placebo, but it was not superior to carvedilol, sotalol or amiodarone. However, the comparison with sotalol has low quality of evidence and was limited by the small number of samples.' One meta-analysis found that carvedilol is better than metoprolol in reducing POAF after cardiac surgery 7, and one review agreed that carvedilol is superior to metoprolol in this regard 8. A meta-analysis reported a greater than 30% risk reduction with sotalol compared with other beta blockers, including metoprolol 26. Physician or cardiothoracic surgeon should be aware of the various beta blockers available in their clinical practice. The selection should be based on the evidence available, for example, studies showed that carvedilol is still superior but in cases when it is not available, then other beta blockers would be of choice.'

2) References: The style seems to be a right form, please check again the instruction for author.

Response from authors: The references were rechecked.

Reviewer: 4

Reviewer Name: Kristen Tecson

Institution and Country: Baylor Heart and Vascular Institute, USA

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Manuscript ID: bmjopen-2020-038364

Title: Metoprolol for prophylaxis of postoperative atrial fibrillation in cardiac surgery patients: systematic review and meta-analysis

Summary: The authors performed a literature search to conduct a meta-analysis to determine the effect of metoprolol on postoperative atrial fibrillation (POAF). The authors conclude that metoprolol is effective in preventing POAF compared with placebo, but not to other treatments. Death and thromboembolism were associated with open heart surgery, but risks were mitigated with metoprolol.

Statistical review: I believe the authors conducted their analyses appropriately and thoroughly, to their best ability. There are limitations to the paper due to limitations of available data; however, they are clearly presented by the authors. Some of those specific concerns are as follows: including both blinded and open label trials, active controls and placebos, IV and oral administration, 8 from Europe and 1 from South America, inconsistent monitoring times, and heterogeneity in certain analyses. I agree with their decision/inability to perform subgroup analyses due to a small number of available trials.

Response from authors: Thank you

Please add explicitly to the text (not just in the table) that the definition of POAF was not the same across trials (some require 1 minute, some 5 minutes, etc.).

Response from authors: We have included the range of post-operative period observed in the Result section.

'POAF was reported as the first occurrence of AF in the post-operative period; however, the period of monitoring was not consistent throughout the trials. It ranges from immediately after surgery until seven days post-operation or discharge from hospital.'

VERSION 2 – REVIEW

REVIEWER	Andrei M. Belyaev Auckland City Hospital
REVIEW RETURNED	16-Aug-2020
GENERAL COMMENTS	<p>Review of the manuscript "Metoprolol for prophylaxis of postoperative atrial fibrillation in cardiac surgery patients: systematic review and meta-analysis" submitted for consideration of publication to BMJ.</p> <p>Comments:</p> <p>1. Tables 2-5 do not have P-values. Therefore, it is difficult to understand the study findings presented in tables.</p>

	<p>2. It is difficult to agree with the authors' statement that "In the metoprolol versus carvedilol comparison, metoprolol increased the risk of POAF compared with carvedilol". This kind of comparison should be based on dosages of metoprolol and carvedilol.</p> <p>3. There is a methodological disadvantage in this paper. The authors searched publications using "the text words 'metoprolol', 'beta blocker' and 'atrial fibrillation' and Boolean operators like AND, OR, truncation and wildcards for variations in words". This strategy yielded very small number of clinical trials to make a meaningful meta-analysis.</p>
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REVIEWER	Isabelle Greiss University of Montreal Hospital Center Canada
REVIEW RETURNED	15-Aug-2020

GENERAL COMMENTS	Previous remarks were addressed. Adequate resubmission.
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REVIEWER	Hiroshi Furukawa Associate Professor Department of Cardiovascular Surgery Tokyo Women's Medical University Medical Center East
REVIEW RETURNED	10-Aug-2020

GENERAL COMMENTS	<p>Dear Author,</p> <p>Thank you for re-submitting manuscript titled "Metoprolol for prophylaxis of postoperative atrial fibrillation in cardiac surgery patients: systematic review and meta-analysis"</p> <p>I have read your successful clinical study with great interest again, and I believe that this manuscript will be worthy to accept for BMJ Open.</p> <p>Thank you for your consideration. If you have any questions and problems, please feel free to ask me ASAP.</p> <p>Reviewer comments This manuscript is well written and revised about the clinical efficacy of Metoprolol for postoperative Af following the reviewers' comments.</p> <p>Additional comments: 1. The size of words seems to be different, please unify. 2. Page 11: focussed → focused</p>
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REVIEWER	Kristen Tecson Baylor Heart and Vascular Institute, USA
REVIEW RETURNED	10-Aug-2020

GENERAL COMMENTS	Thank you for addressing previous comments. Please add the term 'meta-analysis' to the abstract methods. No further comments
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VERSION 2 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 3

Thank you for re-submitting manuscript titled "Metoprolol for prophylaxis of postoperative atrial fibrillation in cardiac surgery patients: systematic review and meta-analysis"

I have read your successful clinical study with great interest again, and I believe that this manuscript will be worthy to accept for BMJ Open.

Reviewer comments

This manuscript is well written and revised about the clinical efficacy of Metoprolol for postoperative AF following the reviewers' comments.

Additional comments:

1. The size of words seems to be different, please unify.

Response from authors: Thank you for the review. We appreciate your effort in doing so. We have standardized the words to Times New Roman, size 12 and double spacing.

2. Page 11: focussed → focused

Response from authors: We have corrected the preferred spelling and rechecked the whole text for consistency of words and spelling.

Reviewer: 4

Thank you for addressing previous comments. Please add the term 'meta-analysis' to the abstract methods. No further comments

Response from authors: Thank you for the review. We have added the term 'meta-analysis' to the abstract as follows:

'This systematic review and meta-analysis aimed to investigate metoprolol compared to other treatments for prophylaxis against POAF.'

Reviewer: 2

Previous remarks were addressed. Adequate resubmission.

Response from authors: Thank you for the review.

Reviewer: 1

1. Tables 2-5 do not have P-values. Therefore, it is difficult to understand the study findings presented in tables.

Response from authors: Thank you for the review. Table 2-5 are products from GRADEpro software and the significance can be assessed based on the confidence interval. We have, however, added the p-values to ease the readers.

2. It is difficult to agree with the authors' statement that "In the metoprolol versus carvedilol comparison, metoprolol increased the risk of POAF compared with carvedilol". This kind of comparison should be based on dosages of metoprolol and carvedilol.

Response from authors: Yes, we agree with the opinion. We have further elaborated the statement in the Result section as below:

'In this comparison, the dose of metoprolol ranged between 50 and 200 mg per day, and carvedilol ranged between 12.5 and 25 mg per day. The heterogeneity of the trials was low at 4% indicating similarities among the trials with regards to population, intervention and comparator of the outcome tested. We did not perform subgroup analysis according to the dosage of drugs due to the limited number of trials, and its indication in the presence of high heterogeneity.'

3. There is a methodological disadvantage in this paper. The authors searched publications using "the text words 'metoprolol', 'beta blocker' and 'atrial fibrillation' and Boolean operators like AND, OR, truncation and wildcards for variations in words". This strategy yielded very small number of clinical trials to make a meaningful meta-analysis.

Response from authors: We have added the following text in the Search strategy section to address this concern:

'The searches for systematic reviews aim to be as extensive as possible to ensure that the review includes as many of the necessary and relevant studies as possible. However, when developing a search strategy, a balance must be struck between striving for comprehensiveness or sensitivity and maintaining relevance or precision. Increasing a search's sensitivity will reduce its precision, and more non-relevant articles will be retrieved 9. We have combined the concepts of population, intervention and study design based on the text words 'metoprolol', 'beta blocker' and 'atrial fibrillation' and Boolean operators like AND, OR, truncation and wildcards for variations in words to have a balance in the sensitivity and precision of the search strategy.'

VERSION 3 – REVIEW

REVIEWER	Hiroshi Furukawa Department of Cardiovascular Surgery Tokyo Women's Medical University Medical Center East
REVIEW RETURNED	15-Sep-2020
GENERAL COMMENTS	<p>Dear Author,</p> <p>Thank you for re-re-submitting manuscript titled "Metoprolol for prophylaxis of postoperative atrial fibrillation in cardiac surgery patients: systematic review and meta-analysis"</p> <p>I have read your successful clinical study with great interest again, and I believe that this manuscript will be worthy to accept for BMJ Open except one correction of abbreviation.</p> <p>Thank you for your consideration. If you have any questions and problems, please feel free to ask me ASAP.</p> <p>Reviewer comments This manuscript is well written and re-revised about the clinical efficacy of Metoprolol for postoperative Af following the reviewers' comments.</p> <p>Additional comments: 1. Table 1. CABG, continuous artery bypass graft → coronary artery bypass graft</p>