Ivabradine versus metoprolol for heart rate reduction in patient ongoing coronary computed tomography angiography: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To compare the efficacy of ivabradine with that of metoprolol for heart-rate-lowering inpatient ongoing coronary computed tomography angiography (CCTA).

METHODS

We systematically searched the electronic database including PubMed, the Cochrane Library, Scopus, UpToDate and Trip Database with no language restriction. The last search was performed on December 2015. In addition, we hand searched the reference lists and relevant articles of all included studies to identify the further studies. The primary outcome was heart rate (HR) reduction between pre-medication and during CCTA inpatient ongoing CCTA who received either ivabradine or metoprolol. We also compared HR reduction between pre-medication and prior CCTA inpatient ongoing CCTA who received either ivabradine or metoprolol.

RESULTS

We included four randomized controlled trials (RCTs) with a total of 455 patients who suspected coronary artery disease (CAD) and ongoing CCTA. Most of the included trials had a low risk of bias. This meta-analysis we found ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA (mean difference (MD) -2.71, 95% CI -3.81 to -1.60, fixed-effect model; I^2=0%). Though comparing pre-medication and prior CCTA, the difference of HR reduction was not statistically significant between ivabradine and metoprolol (MD -2.46, 95% CI -7.34 to 2.41, random-effect model; I^2=93%). For the meta-analysis of the two studies that were high quality, we found that ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA (MD -2.64, 95% CI -6.54 to -0.74, fixed-effect model; I^2=0%).

CONCLUSION

Ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA.

INTRODUCTION

Coronary computed tomography angiography (CCTA) is a non-invasive equipment studying the images of the coronary vessels.[1–6] If the patient's heart rate (HR) over 70 beats per minute (bpm), it would reduce the visibility of the study.[7–10] The Society of Cardiovascular Computed Tomography Guideline recommended to administer 50 mg of metoprolol in patients with baseline HR over 55 bpm, but less than 65 bpm and blood pressure (BP) over 90 mmHg for reducing HR during the scan.[11] Ivabradine is a heart rate lowering drug that selectively inhibits sinus node pacemaker activity.[12–16] It is used as an alternative drug because of rapidly reduce HR to reach the target and make patients exposure minimal radiation during CCTA.[17] However, there are some randomized controlled trials (RCTs) comparing the HR reduction between ivabradine and metoprolol in patients who ongoing CCTA, but not all studies provided the similar results.[18,19] For instance, a previous two Turkish studies in 2012 stated that Ivabradine has the deduction of HR than that of metoprolol when pre-medication compare with during CCTA ivabradine could reduce HR 14 bpm and metoprolol could reduce HR 9 bpm thus they concluded that ivabradine could be used as alternatives drug in patients ongoing CCTA.[20,21] Moreover, an Austrian study in 2012 stated that there was no difference in relation to HR reduction between ivabradine and metoprolol in patient ongoing CCTA.[19] On the contrary, an Indian study in 2012 stated that ivabradine was able to lower the HR than that of metoprolol.[18] We, thus, conducted a systematic review to compare the HR reduction between ivabradine and metoprolol in patient ongoing CCTA.

METHODS

We conducted a systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[22] for reporting this systematic review.

ELIGIBILITY CRITERIA

TYPES OF STUDY

We included all RCTs that compared the HR reduction between ivabradine and metoprolol in patients who ongoing CCTA.

TYPES OF PARTICIPANTS

Any age of patients with normal sinus rhythm who suspected coronary artery disease (CAD) and ongoing CCTA was included in this review.

TYPES OF INTERVENTIONS

Ivabradine and metoprolol were used for reducing HR in patients who ongoing CCTA.

TYPES OF OUTCOMES

The outcomes were (i) HR reduction between pre-medication and during CCTA and (ii) HR reduction between pre-medication and prior CCTA in patients who received either ivabradine or metoprolol. The mean heart rate during CCTA was recorded. The adverse events were recorded.

INFORMATION SOURCES

We systematically searched the electronic database including PubMed, the Cochrane Library,

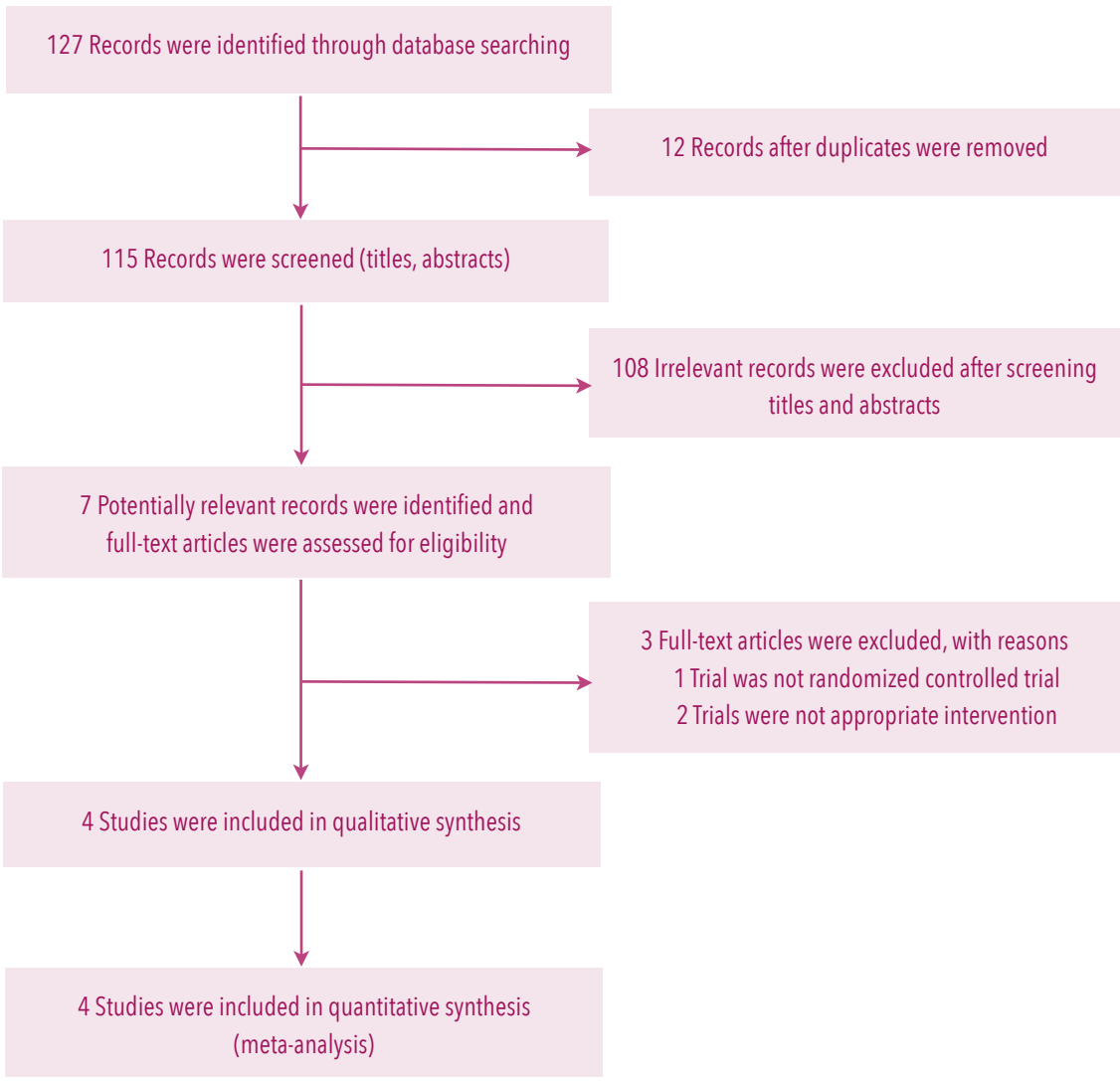

Figure 1. Process of study selection

Scopus, UpToDate and Trip Database with no language restriction. The last search was performed on December 2015. In addition, we hand searched the reference lists and relevant articles of all included studies to identify the further studies.

SEARCH STRATEGIES

We used an integration of keywords to search in Pubmed using MeSH terms "ivabradine" and "metoprolol" and "coronary angiography", "ivabradine" and "metoprolol", "ivabradine" and "coronary angiography", "metoprolol" and

Table 1. Characteristics of studies included in the analysis

Study	N	Study duration (month)	Details of participants	Interventions	Outcomes
Adile 2012	100	N/R	Suspected CAD	Group 1: oral ivabradine 5 mg BID at least 48 hrs Group 2: oral metoprolol 50 mg BID at least 48 hrs If the HR on arrival was >65 bpm, the patients would receive additional doses of the drugs (one dose of either 5 mg ivabradine or 50 mg of metoprolol). If the HR was still >65 bpm 3 hour after the additional first dose, another dose of 5 mg ivabradine or 50 mg metoprolol was administered.	Ivabradine has statistically significant deduction of HR between pre-medication and during CCTA (MD -2.5, 95% CI -4.3 to -0.7) than that of metoprolol as well as when compared pre-medication with prior CCTA (MD -7.7, 95% CI -10.3 to -5.1).
Bayraktutan 2012	110	3	Suspected CAD	Group 1: oral ivabradine 5 mg BID for 3 days Group 2: intravenous metoprolol 5 mg/ml bolus	Ivabradine has statistically significant deduction of HR between pre-medication and during CCTA (MD -3.0, 95% CI -5.0 to -1.0) than that of metoprolol as well as when compared pre-medication with prior CCTA (MD -4.0, 95% CI -6.6 to -1.4).
Celik 2014	125	12	Suspected CAD or mild or moderate-risk of coronary disease or progression of CAD	Group 1: oral ivabradine 15 mg single dose Group 2: initial intravenous metoprolol 5 mg was administered. If the HR was >65 bpm during a test breath hold command immediately prior the scan, an additional 5 mg intravenous metoprolol was administered in addition to the initial 5 mg. No additional dose was administered after the total dose of 10 mg intravenous metoprolol.	Ivabradine has statistically significant deduction of HR between pre-medication and during CCTA (MD -3.0, 95% CI -5.1 to -0.9) than that of metoprolol as well as when compared pre-medication with prior CCTA (MD -3.0, 95% CI -5.4 to -0.6).
Pichler 2012	120	N/R	Suspected CAD or progression of CAD	Group 1: oral ivabradine 15 mg Group 2: oral metoprolol 50 mg If the HR was >60 bpm during a test breath hold command immediately prior the scan, additional medication (5 to 20 mg metoprolol) was administered intravenously until a HR of ≤60 bpm was reached. Moreover, all patients received 0.8 mg nitroglycerin sublingually before the examination.	The difference of HR reduction was not statistically significant between ivabradine and metoprolol between pre-medication and during CCTA (MD -2.0, 95% CI -5.2 to 1.2). But ivabradine has statistically significant deduction of HR between pre-medication and prior CCTA (MD 5.0, 95% CI 2.1 to 8.0) than that of metoprolol.

N/R, not reported; CAD, coronary artery disease; BID, bis in die; HR, heart rate; bpm, beat per minute; CCTA, Coronary computed tomography angiography; MD, Mean difference; CI, confidence interval

Table 2. Jadad Scale

Study	Adile 2012	Bayraktutan 2012	Celik O 2014	Pichler 2012
How the study explained as randomized ?	1	1	1	1
What was the study explain how to create a sequence of randomize? Was it appropriate?	0	0	1	1
Was the study explained as double-blind?	0	0	0	0
Was the double-blind explained the method? Was it appropriate?	0	0	0	0
Had there a detail of withdrawals and dropouts?	1	1	1	1
Scale	2	2	3	3

"coronary angiography" and used keyword "ivabradine CT angiography", "metoprolol CT angiography" as well as in the Cochrane Library. We also used the search term "ivabradine" and "metoprolol" and "coronary angiography" for Scopus. For other databases, we used the following keywords: ivabradine and coronary computed tomography angiography as well as their synonyms for searching.

SELECTION OF STUDIES

Four authors screened titles and abstracts of relevant studies and independently selected of included trials depend on full texts assessment. If disagreement opinion occurred, consensus between four authors was used to resolve.

DATA EXTRACTION AND QUALITY ASSESSMENT

Four authors independently extracted the data from the included studies. We extracted author, year of publication, number of participants, study duration, details of participants, interventions and outcomes. We used the Jadad scale for assessing the quality of selected articles in term of randomization, blinding and an account of all patients. If the scale was 3 or more, the study was considered as a good quality study. We used the Cochrane Collaboration's tool[23] for independently evaluating the risk of bias of the included RCTs. Criteria for judging the risk of bias explained in Part 2; Chapter 8 of The Cochrane Handbook for Systematic Reviews of Interventions was used. The criteria consist of sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other of bias. The result was classified as "high, unclear or low risk of bias".

DATA ANALYSIS

To standardize our outcome, we computed the mean difference (MD) with 95% confidence interval (CI) for continuous data in each group for every trial. The chi-square and I^2 statistics were

Figure 2. Risk of bias
Panel A, risk of bias summary and Panel B, risk of bias graph.

used to evaluate statistical heterogeneity across trials. The statistical test of heterogeneity was significant if $P<0.05$ and heterogeneity was considered high if the I^2 were more than 50%. We also used sensitivity analysis for disregarding studies that were poor quality. In our meta-analysis, we used both the fixed-effect model and random-effect model according to heterogeneity for the analysis. All analyses were performed with Revman 5.3 (RevMan, the programme provided by the Cochrane Collaboration) statistical software.

RISK OF BIAS ACROSS STUDIES

The funnel plot was used to identify publication bias.

RESULTS

Our search strategies recognized 127 publications, 12 were removed due to duplication, 108 were excluded in the first round of assessment because titles and abstracts were not relevant (Figure 1).

Further three publications were excluded by discussion in the second round of assessment because they did not match with our inclusion criteria; the one trial was not RCTs and the two trials did not match our intervention. The remaining four records were included in the qualitative analysis and included in the meta-analysis.

STUDY CHARACTERISTICS

We identified and included 4 RCTs with 455 patients who suspected CAD and ongoing CCTA. Details of all included trials are shown in Table 1. All trials compared the HR reduction between ivabradine and metoprolol in patients who ongoing CCTA. Three were published in 2012 and one in 2014.

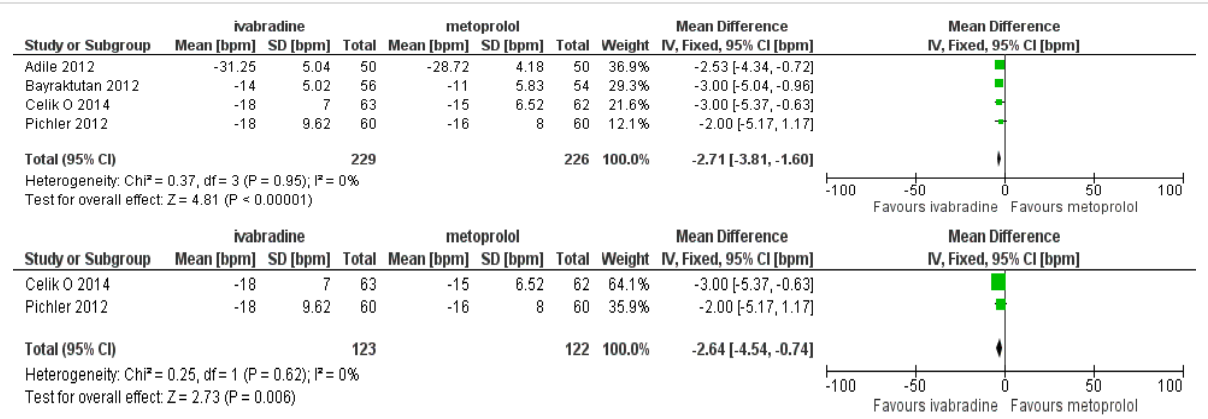

Figure 3. The forest plot of comparison: HR reduction between pre-medication and during CCTA inpatient who used ivabradine and metoprolol

QUALITY AND RISK OF BIAS

The quality of all studies was assessed using the Jadad scale (Table 2). The two trials were poor quality. Moreover, Figure 2 summarize the assessment of the risk of bias for individual trials (domain based-evaluation) using Cochrane Collaboration's tool.[23] Sequence generation process was appropriate in the two trials thus we classified as low-risk selection bias but the one trial was high risk and the one trial was an unclear risk. All trials did not explain concealment or how to conceal thus they were classified as an unclear risk. All trials did not explain the blinding of participants thus we classified as an unclear risk. The three trials did not describe tools for measuring the outcome but we considered that the outcome was not disturbed despite lack of blinding hence they were classified as low risk. All the trials did not have missing outcome data thus they were classified as low risk of attrition bias. All

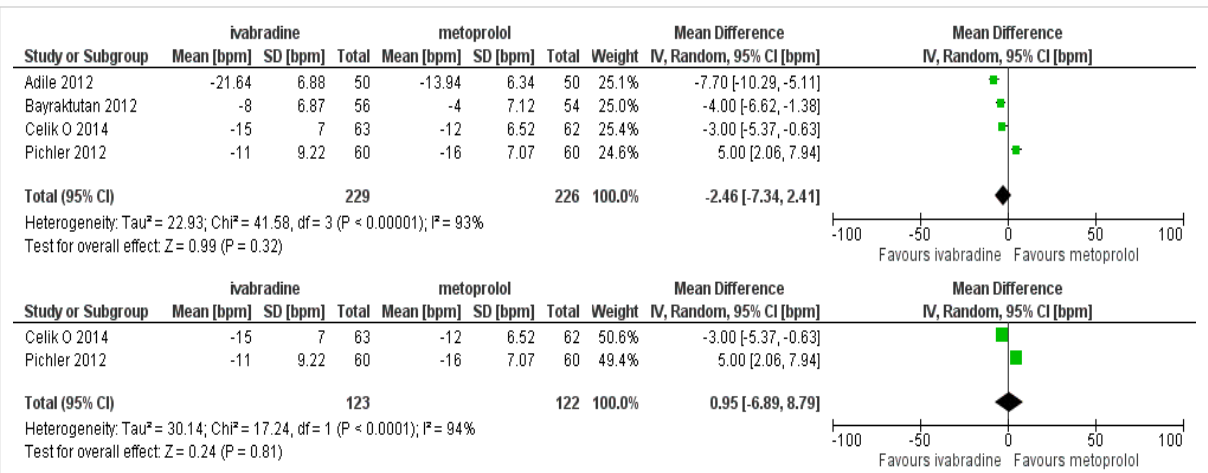

Figure 4. The forest plot of comparison: HR reduction pre-medication and prior CCTA inpatient who used ivabradine and metoprolol

Table 3. The mean HR during CCTA

Study	Ivabradine	Metoprolol
Adile 2012	58.8±1.3	63.2±1.4
Bayraktutan 2012	59.0±4.1	64.0±6.7
Celik 2014	62.0±7.0	66.0±6.0
Pichler 2012	58.0±8.0	60.0±8.0
Average	59.5±5.7	63.3±6.1

Plus–minus values are means ±SD.

trials reported pre-specified outcomes, we, then, classified them as low risk of reporting bias. The one trial did not classify other biases thus we classified as unclear risk and the one trial was classified as high risk.

PRIMARY OUTCOME

The four trials with a total of 455 patients were contributed to the meta-analysis of (i) HR reduction between pre-medication and during CCTA and (ii) HR reduction between pre-medication and prior CCTA in patients who received either ivabradine or metoprolol. Ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA (MD -2.71, 95% CI -3.81 to -1.60, fixed-effect model; I^2=0%) (Figure 3). Though comparing pre-medication and prior CCTA, the difference of HR reduction was not statistically significant between ivabradine and metoprolol (MD -2.46, 95% CI -7.34 to 2.41, random-effect model; I^2=93%) (Figure 4).

SENSITIVITY ANALYSIS

The meta-analysis of the two studies that were high quality, we found that ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA (MD -2.64, 95% CI -6.54 to -0.74, fixed-effect model; I^2=0%) (Figure 3). Though comparing pre-medication and prior CCTA, the difference of HR reduction was not statistically significant between ivabradine and metoprolol (MD 0.95, 95% CI -6.89 to 8.79, random-effect model; I^2=94%) (Figure 4). The results were similar to the meta-analysis of the four study, so we concluded that the poor quality studies did not affect the results.

HEART RATE DURING CCTA

Table 3. shows HR during CCTA; The mean heart rate was 59.5±5.8 bpm for patients who used ivabradine and 63.3±6.1 bpm for patients who used metoprolol. Both ivabradine and metoprolol could reduce HR to target which less than 70 bpm.

ADVERSE EVENTS

Table 4. shows the adverse events in the four studies; one case experienced hypotension and six cases experienced a visual disturbance in patients who received ivabradine whereas one case experienced hypotension in patients who received metoprolol.

Table 4. Adverse events in randomized controlled trials of this review

Study	Trial arm	No. of adverse events		
		Bradycardia	Hypotension	Visual disturbance
Adile 2012	Ivabradine (n=50)	0	0	N/R
	Metoprolol (n=50)	0	0	N/R
Bayraktutan 2012	Ivabradine (n=56)	0	1	1
	Metoprolol (n=54)	0	1	0
Celik 2014	Ivabradine (n=63)	0	0	1
	Metoprolol (n=62)	0	0	0
Pichler 2012	Ivabradine (n=60)	0	0	4
	Metoprolol (n=60)	0	0	0

N/R=not report

RISK OF BIAS ACROSS

Figure 4 shows the potential of publication bias that was identified by using a funnel plot. The funnel plot of the four trials included in the meta-analysis appeared to be asymmetrical as there were not many studies to be included.

DISCUSSION

STUDY SUMMARY EVIDENCE

The four trials with a total of 455 patients were contributed to the meta-analysis of HR reduction in patient who received either ivabradine or metoprolol, we found that ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA but though comparing pre-medication and prior CCTA, the difference of HR reduction was not statistically significant between ivabradine and metoprolol. For adverse events; one case experienced hypotension and six cases experienced a visual disturbance in patients who receive ivabradine whereas one case experienced hypotension in patients who received metoprolol.

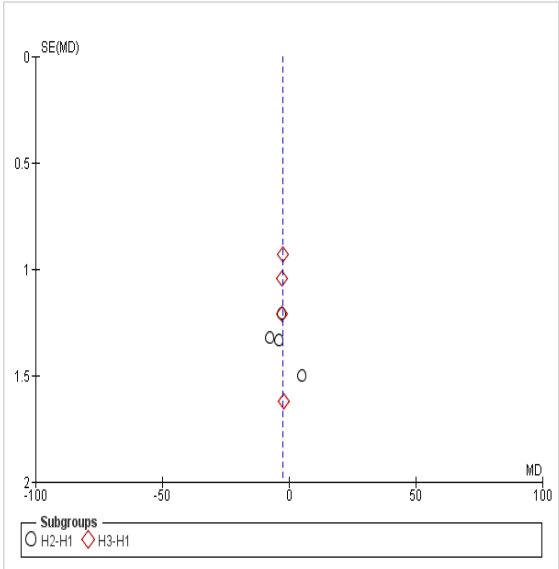

Figure 4. Funnel plot based on mean difference for HR reduction

COMPARISON WITH OTHER STUDIES

Our study found that ivabradine was superior over metoprolol, a beta-blocker in term of heart rate reduction. The findings were similar to an Italian study in 2012 stated that the rate of patients achieved the target heart rate in ivabradine 7.5 mg was higher than that of atenolol another beta-blocker.[24] Several minor adverse events were reported in our review. Many studies have reported the incidence of serious adverse events found higher in a group with ivabradine than that of placebo in stable CAD. These consisted of bradycardia, visual disturbance, and atrial fibrillation.[25-27] The study in 2009 show vasovagal reaction was found in patients who received oral or intravenous metoprolol,[28] but did not found the vasovagal reaction in our study.

STRENGTHS AND LIMITATIONS OF REVIEW

Our study is the first systematic review that described (i) HR reduction between pre-medication and during CCTA and (ii) HR reduction between pre-medication and prior CCTA in patients who received either ivabradine or metoprolol. However, our meta-analysis has limitations. The daily dose and duration of administration were various among the four studies.

Our systematic search had no dose limitation and thus allowed us to search for all dose ranges. There was a small number of included studies with the different outcome thus when we systematically included studies they were high heterogeneity and cause adverse events reported as minimal. The other limitation is a risk of bias in some of the included studies. The one study had many unclear risks of bias, the one study had a high risk of bias of random sequence generation and the one study had a high risk of bias of reporting. Others limitation was quality of studies, there are the two studies had poor quality when evaluated by Jadad scale. Another limitation is methodological heterogeneity among included studies. None of the included studies identified point of time for calculating the HR reduction thus we calculated the HR reduction from means and standard deviations that reported in included studies.

CONCLUSION

Ivabradine had a statistically significant reduction of HR more than that of metoprolol inpatient ongoing CCTA comparing pre-medication and during CCTA. But in clinical practice, both ivabradine and metoprolol can reduce HR to reach the target. When comparing pre-medication and prior CCTA, the difference in HR reduction was not statistically significant between ivabradine and metoprolol. We recommend that ivabradine can be used as an alternative heart rate-lowering agent in patients who have the contraindication to beta-blocker. For further study, we suggest having the new study that clear study design in relation to allocation concealment and blinding with long-term assessment of the adverse events.

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COMPETING INTERESTS: This study has no competing on interest.
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