

Blood pressure lowering effect of calcium channel blockers on perioperative hypertension

A systematic review and meta-analysis

Yu Lin, MM*, Lina Ma, MM

Abstract

Background: Acute perioperative hypertension has been associated with poor outcomes of surgery, and the role of calcium channel blockers (CCB) on controlling perioperative blood pressure (BP) remains controversial. Thus, this meta-analysis was designed to assess the efficacy and safety of CCB in treating perioperative hypertension compared with other antihypertensive agents.

Methods: PubMed, Medline, Cochrane, and EMABSE databases was systematically searched up to January 2018 for randomized control trials (RCTs) or other control studies comparing the efficacy of CCB versus other antihypertensive medicines for perioperative hypertension modulation. The efficacy and safety of CCB in treating perioperative hypertension were assessed through pooling mean difference (MD) with its 95% confidence interval (CI) or risk ratio (RR) with its 95% CI.

Results: In total, 14 studies were included in the meta-analysis. There is no significant difference regarding successful treatment (RR=2.64, 95% CI: 0.95, 7.29; $I^2=97%$, $P<.05$), systolic blood pressure (SBP) (MD=-7.05, 95% CI: -16.27, 2.17; $I^2=78%$, $P<.05$), overall adverse events (RR=0.88, 95% CI: 0.66, 1.16; $I^2=54%$, $P=.02$), atrial fibrillation (RR=0.80, 95% CI: 0.60, 1.07; $I^2=32%$, $P=.20$) and heart rates (MD=-1.05, 95% CI: -7.81, 5.71; $I^2=84%$, $P<.05$) between patients treated by CCB and other drugs. In the subgroup analysis, statistical significance can be observed regarding successful treatment (RR=3.46, 95% CI: 1.67, 7.18; $I^2=84%$, $P<.05$) and postoperative SBP (MD=-9.98, 95% CI: -20.03, 0.08; $I^2=97%$, $P<.05$) in the RCTs subgroup.

Conclusion: CCB was highly effective and well tolerated for treating perioperative hypertension.

Abbreviations: BP = blood pressure, CCB = calcium channel blockers, CI = confidence interval, MD = mean difference, NOS = Newcastle-Ottawa Scale, RCTs = randomized control trials, RR = risk ratio, SBP = systolic blood pressure.

Keywords: calcium channel blockers, hypertension, meta-analysis, perioperative period

1. Introduction

According to a report by the Centers for Disease Control and Prevention, 1 of every 3 Americans has hypertension,^[1] which represents one of the most prevalent pathology worldwide. And perioperative blood pressure (BP) has been recognized as one of the main factors associated with worse outcomes, such as acute end-organ damage.^[2] Up to 80% of patients undergoing cardiac surgeries and 25% of patients undergoing non-cardiac procedures was affected by acute perioperative hypertension.^[3] Moreover, the performance of surgery might be postponed when pre-existing hypertension occurred.

Calcium channel blockers (CCBs) are a kind of drug inhibiting the flow of extracellular calcium through ion-specific channels that span the cell wall. There are 2 kinds of frequently used CCB with different effects on vasodilation and myocardium inotropism. One is dihydropyridines including clevidipine, amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, and nisoldipine, which decreases BP by dilating arterial vascular tree. Another is nondihydropyridines including diltiazem, and verapamil, which perform by reducing heart rate, contractility, and slightly increasing arteriodilation.^[4] As the development of technology, some new drug belongs to CCB has been researched.^[5]

The BP-lowering effect of CCB combinations are supported by long-term evidence, but CCB has not yet been widely used in clinical practice.^[6] Several studies have shown the potency of CCB in BP maintenance.^[7] For example, by meta-analysis, Espinosa et al put forward that clevidipine play highly effective role for management of perioperative arterial hypertension.^[8] Additionally, other CCBs, such as nicardipine and peridipine, has also been assessed the role of managing perioperative arterial hypertension in clinical evidence.^[9] However, CCB has not been assessed as a whole for its role in hypertensive management.

In this study, we hypothesized that CCB was a better kind of medicine for lowering BP on perioperative hypertension comparing with other antihypertensive agents. Thus, this meta-analysis was designed to assess the efficacy and safety of CCB in treating perioperative hypertension compared with other antihypertensive agents.

Editor: Yan Li.

YL and LM contributed equally to this work.

The authors report no conflicts of interest.

Cardiovascular Department, Tianjin Nankai Hospital, Tianjin, China.

* Correspondence: Yu Lin, Tianjin Nankai Hospital, No.122, Sanwei Road, Nankai District, Tianjin, China, 300100 (e-mail: yulinytjnk@sina.com).

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Medicine (2018) 97:48(e13152)

Received: 25 April 2018 / Accepted: 15 October 2018

<http://dx.doi.org/10.1097/MD.00000000000013152>

2. Material and methods

This article was undertaken followed the PRISMA Guidelines for meta-analysis. Since this is a meta-analysis, ethical approval is no applicable.

2.1. Search strategy

Relevant articles published in English before January 2018 were systematically searched throughout PubMed, Medline, Cochrane, and EMABSE databases. The main key words used for the search were as follows: “Calcium channel blockers” or “CCB” or “nifedipine” or “amlodipine” or “lercanidipine” or “nimodipine” or “nicardipine” or “nitrendipine” or “nisoldipine” or “felodipine” or “benidipine” or “lacidipine” or “barnidipine” or “lercanidipine” or “clevidipine” or “benzothiazole” or “diltiazem” or “phenylalkylamines” or “verapamil” or “triphenylpiperazine” or “siberlium” or “flunarizine” or “cinnarizine” or “lidoflazine” and “blood pressure” or “hypertension”.

2.2. Selection criteria

Randomized control trials (RCTs) or non-randomized control trials (non-RCTs) published in English conforming to the following selection criteria were enrolled in the meta-analysis:

- (1) patients were diagnosed with hypertension during the surgery;
- (2) the efficacy of CCBs in BP control during perioperative period was evaluated;
- (3) adverse events regarding the treatment were reported;
- (4) treatment success was defined as the ability to decrease systolic blood pressure (SBP) by 15% from baseline in the study.^[10]

Studies would be excluded if data within could not be used for statistical analysis. In addition, the non-original studies included reviews, letters, and comments were also excluded.

All titles and abstracts from the initial search were screened by reviewers. If the title and abstract did not contain enough information to include or excluded the study from the analysis, the study was reviewed in full-text. Citation lists of relevant articles and reviews were additionally scanned to identify further studies of interest.

2.3. Data extraction and quality assessment

Data extraction was performed by the 2 investigators independently, and the extraction form was previously designed. Discrepancies were resolved by referring the original articles. The information, including the first author's name, year of publication, number, and age of the enrolled patients, region, follow-up duration, the design of the included trails, and intervention method was extracted.

According to the Cochrane Handbook of Systematic Review of Interventions, RCTs were assessed by using Review Manager 5.3 based on seven perspectives (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and others) and scored as unclear, low, or high risk of bias (Fig. 1). The Newcastle-Ottawa Scale (NOS) with a maximum of 9 points was applied to evaluate the quality of non-RCTs with three categories for scoring: selection of the study groups, quality of the

adjustment for confounding and ascertainment of the outcome of interest in the cohorts.

2.4. Statistical analyses

Statistical analyses were performed by Review Manager 5.3 (The Nodic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). Dichotomous data were analyzed by risk ratio (RR) for RCTs and odd ratio (OR) for non-RCTs with its 95% confidence interval (CI), including the prevalence of successful success rate and the rate of adverse events occurrence. Continuous data were analyzed by mean difference (MD) with its 95% CI. Heterogeneity among individual studies was examined by Cochran's Q statistic and I^2 test. Significant heterogeneity occurred if P value $<.05$ (Q statistic) and/or $I^2 > 50\%$, and then the random effects model was selected, otherwise, the fixed effect model would be used. Sensitivity analysis was performed to confirm the robustness of the results through omitting 1 study at a time.

3. Results

3.1. Studies selection

As shown in Figure 2, according to the search criteria, 15899 articles were identified and 6630 were originally enrolled, with 6619 from database searching and 11 from manual searching in citation lists. In total, 1432 articles were remained after eliminating duplicates and obvious irrelevance. After that, 1241 studies were excluded for non-control studies and low relevance. Then 47 articles were fully assessed. After checking the full texts, 33 articles were excluded, including 20 articles without raw data and 13 articles without valuable endpoints. Finally, 14 eligible studies were included in this meta-analysis.^[7,10–22]

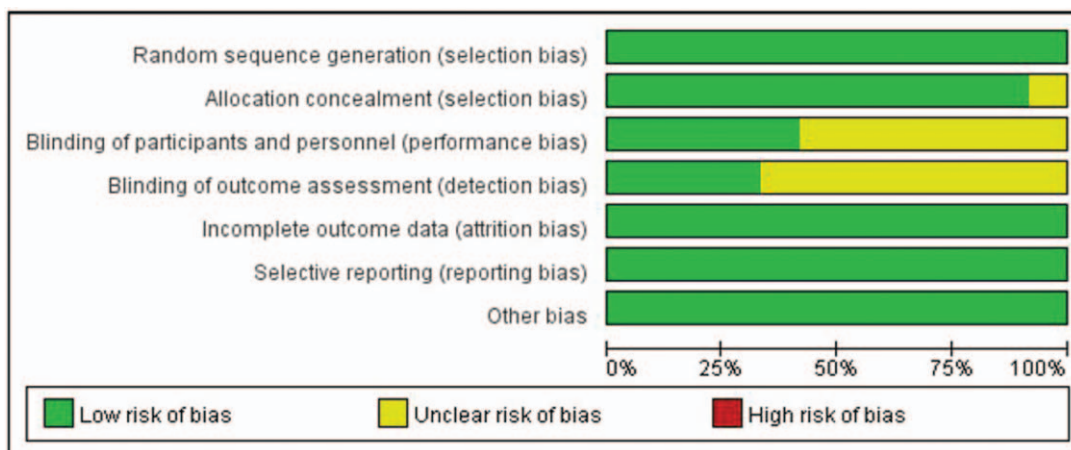
3.2. Characteristics and quality of the enrolled studies

Table 1 shows the basic information of the meta-analysis. All included studies were published from 1986 to 2015. Among the enrolled 14 studies, patients in 7 studies were from America. 6 studies researched on clevidipine, 2 studies on nicardipine or peridipine, 3 studies on diltiazem, 2 studies on nifedipine, 3 studies on verapamil. Most of the control groups of the included studies received placebo. In addition, four studies were multi-center studies. Twelve studies were assessed by Revman 5.3, and risk of bias in all studies is low. Only 2 studies are non-RCTs assessed by NOS, and the scores were all more than 5.

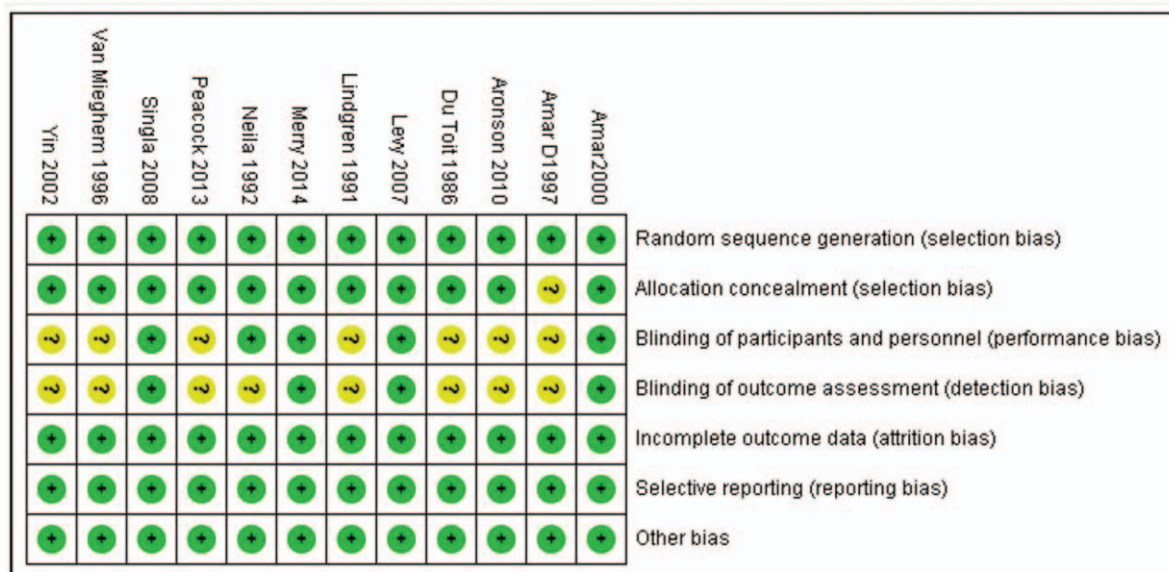
3.3. Analysis of antihypertensive effect: CCB versus control

Four studies^[10,12,16,17] with a total of 449 participants reported the number of patient with successful treatment. As shown in Figure 3.1, significant heterogeneity was observed among enrolled studies ($I^2=97\%$, $P<.05$), therefore effect size was pooled under random effects model. There is no significant difference between CCB and the control group (RR=2.64, 95% CI: 0.95, 7.29).

Four studies^[14,15,17,20] with a total of 1743 participant reported postoperative SBP, as shown in Figure 3.2. Significant heterogeneity was observed among the enrolled studies ($I^2=78\%$, $P<.05$), therefore effect size was pooled under random effects model. No significant difference was detected in patients



Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 1. Bias assessment of RCTs. Low risk of bias can be detected across all the studies. RCT=randomized control trial.

treated by CCB versus patients treated by other antihypertensives (MD = -7.05, 95% CI: -16.27, 2.17).

3.4. Adverse events

Ten studies^[10-14,17-19,21,22] with a total of 1231 participants reported overall adverse events. Significant heterogeneity occurred among the enrolled studies ($I^2=54\%$, $P=.02$), therefore random effects model was adopted. No significant difference was observed on adverse events for hypertensive patients treated by CCB versus other strategies (RR=0.88, 95% CI: 0.66, 1.16). The result remained unchanged after sensitivity analysis. Details are shown in Figure 4.1. Since there are enough studies regarding overall adverse events, we generated a funnel plot to visualize the bias and heterogeneity. As shown in Figure 5, the distribution of the studies is very symmetric indicating low risk of bias and heterogeneity, except the study by Lindgre.

Six studies with a total of 1224 participants reported atrial fibrillation, which is one of the most common adverse events. No significant heterogeneity was found ($I^2=32\%$, $P=.20$), therefore fixed effects model was used. There no statistical difference was observed between the two groups regarding the prevalence of atrial fibrillation ((RR=0.80, 95% CI: 0.60, 1.07). However, the diamond of pooled point would favor CCB group and the heterogeneity would be less if excluded Singla et al's study^[12] (RR=0.72, 95% CI: 0.53, 0.99, $I^2=3\%$, $P=.39$). Details are presented in Figure 4.2.

Six studies^[7,11,12,14,16,21] with a total of 569 participants referred heart rate after surgery. Significant heterogeneity was observed among studies ($I^2=84\%$, $P<.05$), therefore random effect model was employed. Figure 4.3 shows that there is no significant difference on heart rates between CCB and other antihypertensive measures (MD=-1.05, 95% CI: -7.81, 5.71), and the result remained unchanged after sensitivity analysis.

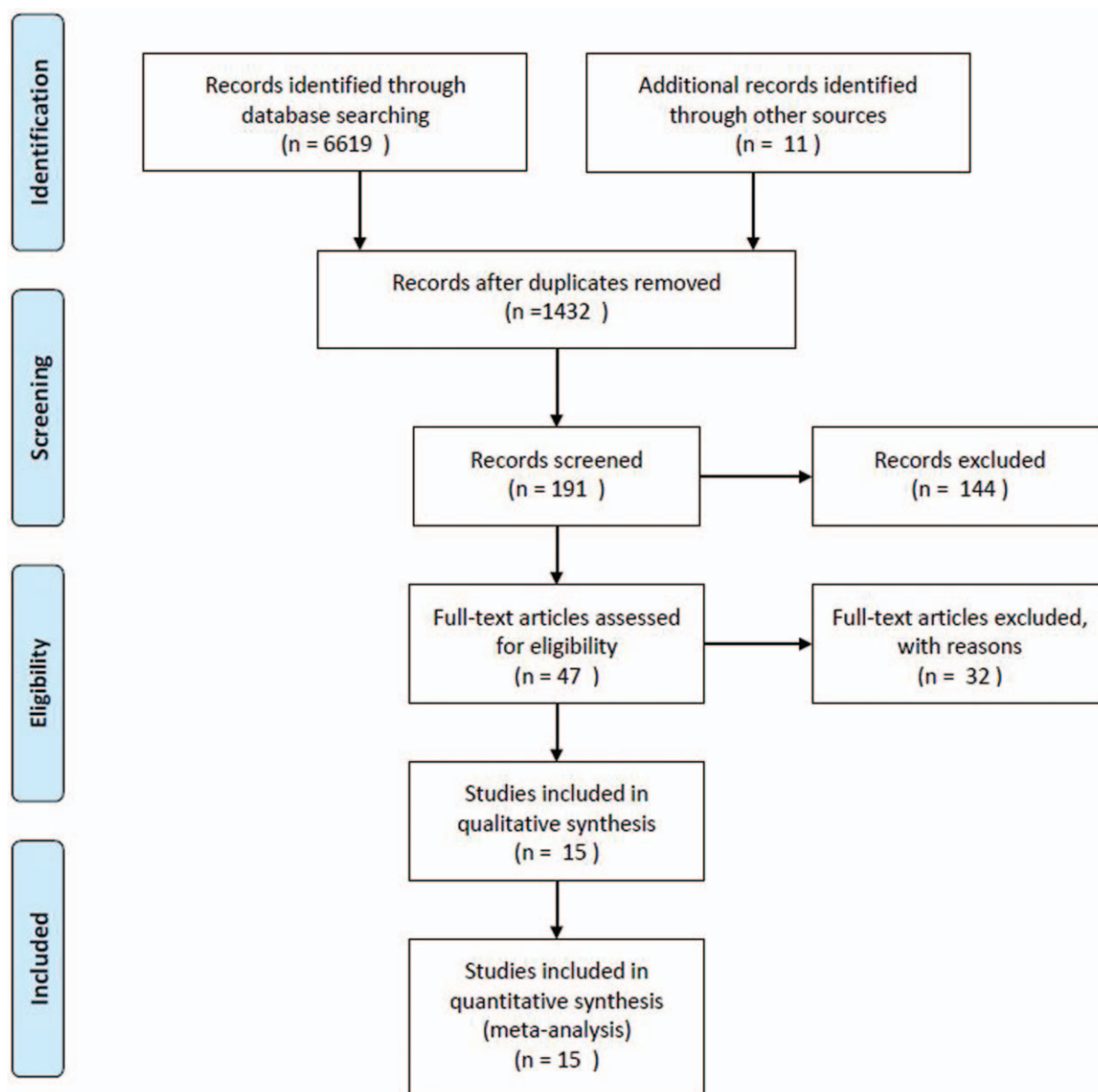


Figure 2. Flow chart of selection process.

3.5. Subgroup analysis

Subgroup analysis was performed by stratified the studies into RCTs subgroup and non-RCTs subgroup. Significant difference can be observed regarding successful treatment ($RR = 3.46$, 95% CI: 1.67, 7.18; $I^2 = 84\%$, $P < .05$) and postoperative SBP ($MD = -9.98$, 95% CI: -20.03 , 0.08 ; $I^2 = 72\%$, $P < .05$) in the RCTs subgroup. However, no significant difference can be detected in terms of total adverse events, atrial fibrillation, and heart rate. Details are presented in Table 2.

4. Discussion

This meta-analysis found that CCB can significantly decreased perioperative BP and would not lead to serious adverse events compared with other antihypertensive drugs, which indicate its high effectiveness and well tolerance in with the treatment of perioperative hypertension.

In the combined analysis of successful treatment and SPB, no significant difference can be detected between the 2 groups, but CCB group still had high prevalence of successful treatment and lower SBP than the control group. Furthermore, in the subgroup analysis by stratified the studies into RCTs and non-RCTs groups, we found that more CCB-treated patients received successful treatment that the SBP was decreased by 15% from the baseline with lower SBP compared with those received other medicines in RCTs subgroup, which was consistent with previous researches.

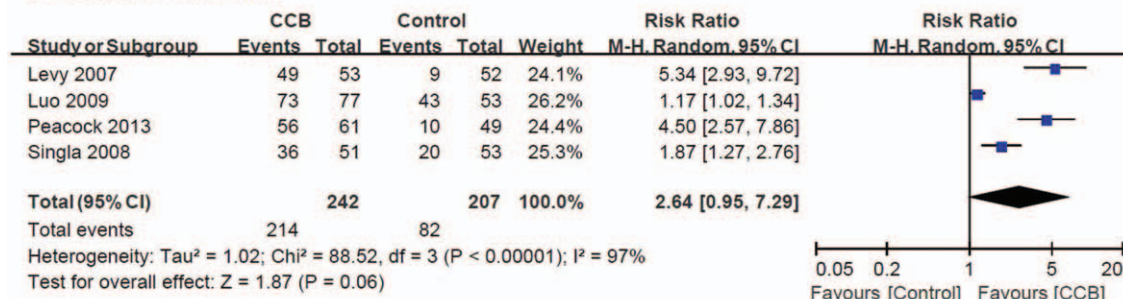
Adverse events were assessed from the time of drug initiation to hospital discharge or 7 days postoperatively. Common adverse effects of CCBs include edema, flushing, headache, dizziness, constipation (particularly with high-dose verapamil), nausea, rash, and drowsiness.^[23,24] Although there is no significant difference between CCB group and the control group regarding overall adverse events, atrial fibrillation, and heart rate, statistical

Table 1
Characteristics of 14 included studies.

Study	Patients	Design	Country	Number	Intervention	Age	Study period	Route of administration	NOS scores
Yin 2002 [7]	Intraoperative hypertension	RCT	China	34	Perdipine versus nitroglycerin	24–78	NA	intravenous	NA
Levy, 2007[10]	cardiac surgery with hypertension	RCT	USA	105	clevidipine (0.4–8.0 0.2–8μg.kg ⁻¹ .min ⁻¹) or 20% lipid emulsion (placebo)	Clevidipine: 65.8 (10.0); Placebo: 61.7 (10.3)	NA	intravenous	NA
Merry, 2014[11]	coronary artery bypass grafting with hypertension	RCT	USA, New Zealand	100	clevidipine (0.2–8 μg.kg ⁻¹ .min ⁻¹) or nitroglycerin (0.4 μg.kg ⁻¹ .min ⁻¹ to a clinician-determined maximum dose rate)	Clevidipine: 65.8 (11.3); Nitroglycerin: 63.2 (12.3)	October 4, 2003 to April 26, 2004	intravenous	NA
Singla, 2008[12]	cardiac surgery postoperative hypertension	RCT	USA	110	clevidipine (0.4–8.0 μg.kg ⁻¹ .min ⁻¹) or 20% lipid emulsion (placebo)	Clevidipine: 63.8 (12.6); Placebo: 62.3 (11.8)	December 2003 and October 2004	intravenous	NA
Amar, 2000[13]	Non-cardiac surgery postoperative hypertension	RCT	USA	330	Diltiazem versus placebo	Diltiazem: 66(10); placebo: 67(10)	February 1997- August 1999	intravenous	NA
Amar, 1997[14]	Non-cardiac surgery postoperative hypertension	RCT	USA	70	Diltiazem versus digoxin	Diltiazem: 57(12); digoxin: 58(12)	February 1994- February 1996	intravenous	NA
Aronson, 2011[15]	cardiac surgery perioperative hypertension	RCT	USA	1507	clevidipine versus an active comparator (NTG, SNP, or NIC)	64.8 (10.78)	NA	intravenous	NA
Luo, 2009[16]	Non-cardiac surgery perioperative hypertension	Non-RCT	China	265	Betaloc versus verapamil and Diltiazem	Betaloc: 68.1 (9.5); CCB: 67.8 (11.8)	March 2003-May 2007	intravenous	6
Peacock, 2013[17]	acute heart failure with hypertensive	RCT	USA (African American)	104	clevidipine versus antihypertensive therapy	61 (14.9)	NA	intravenous	NA
Du, 1986[18]	Hip-replacement surgery perioperative hypertension	RCT	South Africa	50	Nifedipine versus placebo	63–84	NA	oral	NA
Neila 1992 [19]	postoperative hypertension	RCT	NA	139	nicardipine with sodium nitroprusside	NA	NA	intravenous	NA
Kimura, 2015[20]	Dental implant-related surgeries preoperative hypertension	Non-RCT	Japan	336	Nifedipine	NA	January 2008- February 2012	oral	7
Lindgren, 1991[21]	Non-cardiac surgery postoperative hypertension	RCT	NA	25	Verapamil versus placebo	Verapamil: 60(8); placebo: 64(9)	NA	oral	NA
Van, 1996[22]	Non-cardiac surgery postoperative hypertension	RCT	Belgium	199	Verapamil versus placebo	Verapamil: 60(12); placebo: 59(11)	NA	intravenous	NA

EPP = extrapleural pneumonectomy, NIC = denotesnicardipine, NTG = nitroglycerine, RCT = randomized control trial, SNP = nitroprusside.

1. Successful treatment



2. SBP after operation

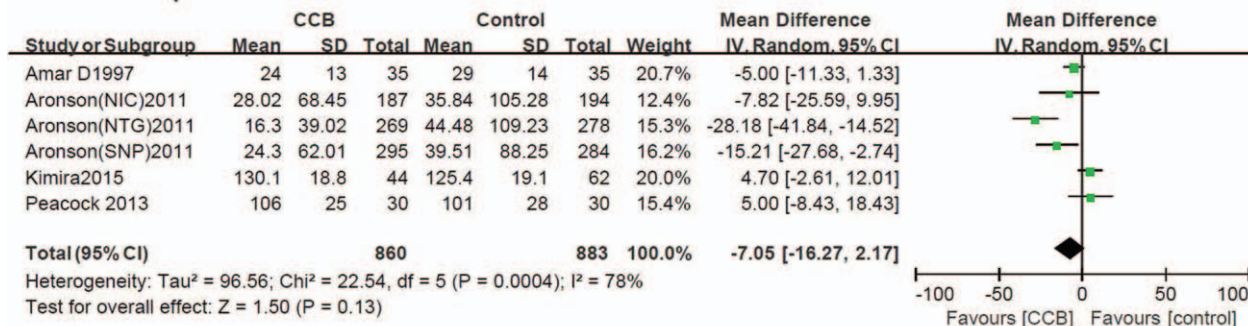
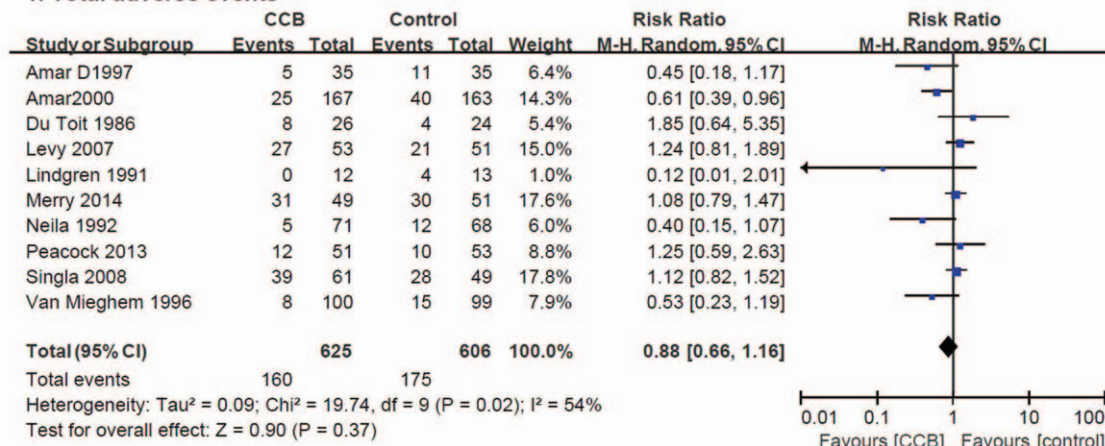
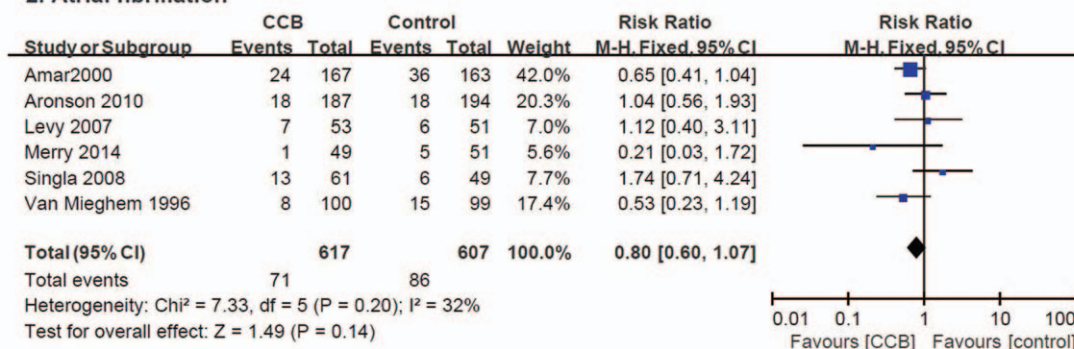


Figure 3. Forest plot of the efficacy of CCBs versus other medicines. Four studies with a total of 449 participants reported the number of patient with successful treatment. Significant heterogeneity was observed among enrolled studies (I² = 97%, P < .05). No significant difference between CCB and the control group (RR = 2.64, 95% CI: 0.95, 7.29). CCB=calcium channel blockers, CI=confidence interval, RR=risk ratio.

1. Total adverse events



2. Atrial fibrillation



3. Heart rates

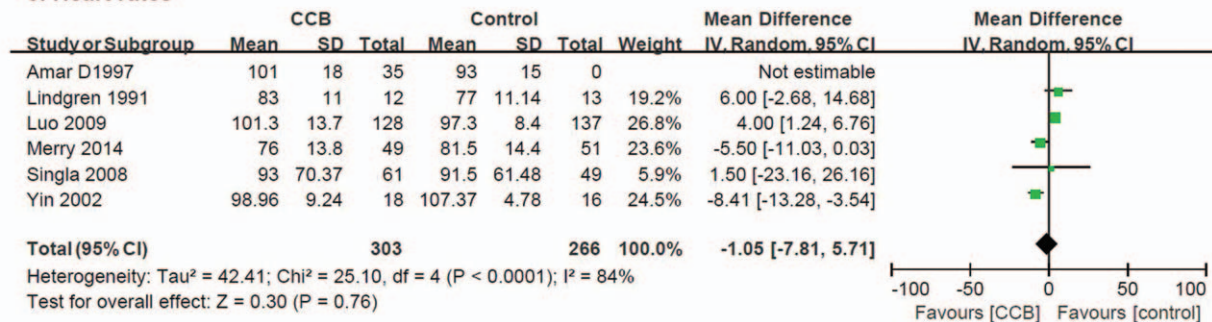


Figure 4. Forest plot of the adverse events of CCBs versus other medicines. 4.1 Total adverse events. Ten studies with a total of 1231 participants reported overall adverse events. Significant heterogeneity occurred among the enrolled studies (I²=54%, P=.02). No significant difference was observed on adverse events for hypertensive patients treated by CCB versus other strategies (RR=0.88, 95% CI: 0.66, 1.16). 4.2 Atrial fibrillation. Six studies with a total of 1224 participants reported atrial fibrillation, which is one of the most common adverse events. No significant heterogeneity was found (I²=32%, P=.20). There no statistical difference was observed between the 2 groups regarding the prevalence of atrial fibrillation (RR=0.80, 95% CI: 0.60, 1.07). 4.3 Heart rates. Six studies with a total of 569 participants referred heart rate after surgery. Significant heterogeneity was observed among studies (I²=84%, P<.05). No significant difference on heart rates between CCB and other antihypertensive measures (MD=-1.05, 95% CI: -7.81, 5.71). CCB=calcium channel blockers, CI=confidence interval, MD=mean difference.

significance can be detected with lower heterogeneity regarding atrial fibrillation if excluded Singal et al's study.^[12] We further went through this study, and a potential explanation for such difference may be the larger population of valvular surgery in the CCB group who were at increased risk for postoperative complications.^[25] As shown in the funnel plot, the study by Lindgren^[21] may higher risk of bias and heterogeneity than other studies, which may account for the small number of patients.

There are some limitations should be noted in this meta-analysis. Although the evaluation criteria was in line with each

other, significant heterogeneity was still observed on most endpoints. The natural condition, including the background of the patients, the technology and experience of the examining doctor, and the dose of the drugs might be one source of such heterogeneity.^[26,27] Moreover, five kinds of CCBs were included in the meta-analysis and different types of drugs may have different antihypertensive efficiency and adverse effect, which may also be the source of heterogeneity. In addition, according to the limited data of included studies, subgroup analysis stratified by the kinds of CCB could not be performed. These limitations

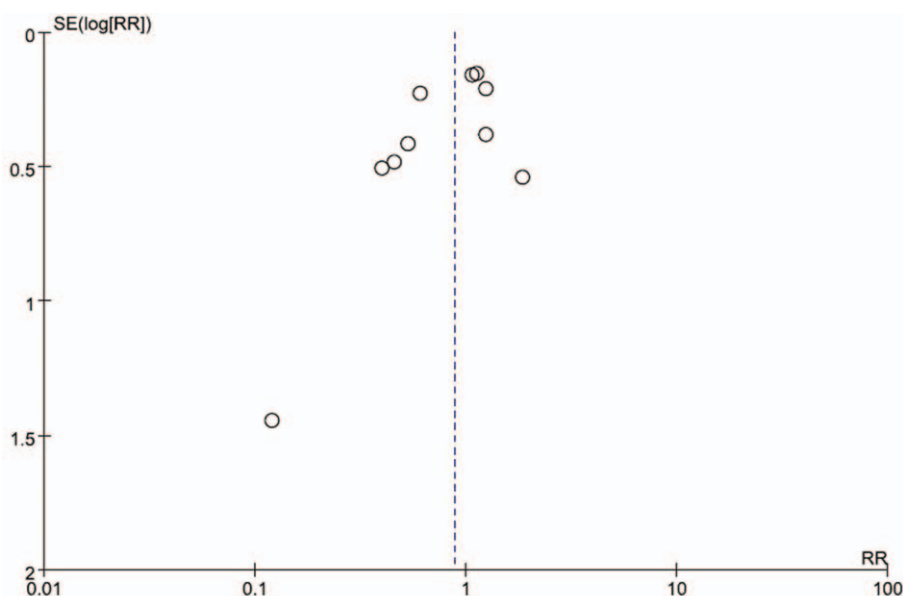


Figure 5. Funnel plot of adverse events. Low risk of bias and heterogeneity can be detected except the study by Lindgre.

Table 2

Subgroup analysis of successful treatment, SBP after operation and heart rate.

Outcome	Subgroup	No. of studies	Effect estimate	Test for overall effect	Heterogeneity
Successful treatment	RCTs*	3	3.46 [1.67, 7.18]	$P < .05$	$I^2 = 84%$ $P < .05$
	Non-RCTs	1	4.24 [1.25, 14.36]	$P = .02$	NA
	Overall	4	2.64 [0.95, 7.29]	$P < .05$	$I^2 = 97%$ $P < .05$
SBP after operation	RCTs*	5	-9.98 [-20.03, 0.08]	$P = .05$	$I^2 = 72%$ $P < .05$
	Non-RCTs	1	4.70 [-2.61, 12.01]	$P = .21$	NA
	Overall	6	-7.05 [-16.27, 2.17]	$P = .02$	$I^2 = 78%$ $P < .05$
Heart rate	RCTs	5	-3.26 [-9.77, 3.24]	$P = .33$	$I^2 = 64%$ $P = .04$
	Non-RCTs	1	4.00 [1.24, 6.76]	$P < .05$	NA
	Overall	6	-1.05 [-7.81, 5.71]	$P = .04$	$I^2 = 84%$ $P < .05$

RCT = randomized control trial; SBP = systolic blood pressure.

*Statistical significance. Risk ratio (RR) was applied to successful treatment; mean difference (MD) was applied to the rest endpoints.

may compromise the reliability of our findings; therefore this study demonstrated the possible effect and adverse events of CCBs on perioperative hypertension.

5. Conclusions

We performed a meta-analysis to assess the efficacy of CCBs in the treatment of perioperative hypertension, and to our knowledge, this is the first meta-analysis with various CCBs on perioperative BP management. Our results demonstrated that CCBs may be effective for treating perioperative hypertension with a good safety profile compared with other medicines, which should be encouraged for hypertensive patients who would undergo surgery.

Author contributions

Conceptualization: Yu Lin.

Data curation: Yu Lin.

Formal analysis: Lina Ma.

Methodology: Lina Ma.

Software: Lina Ma.

Writing – original draft: Yu Lin.

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