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The Safety of Calcium Channel Blockers in Controlling Blood Pressure During Cardiac Surgery: A Meta-analysis of Random Controlled Trials

Xueming Chen [1], Shiyan Chen [2], Zecheng Yang [1, *]

[1] Department of Anesthesiology, Panyu Hospital of Chinese Medicine, Guangzhou, Guangdong 511400, China
[2] Department of General Surgery, Panyu Hospital of Chinese Medicine, Guangzhou, Guangdong 511400, China
[*] **Corresponding author**: Zecheng Yang (Email: 519246774@qq.com)

Abstract: Background: Intraoperative hypertension is a very common critical condition in cardiac surgery, which may lead to myocardial ischemia, affect the smooth progress of the operation, and even lead to the death of the patient. Therefore, it is necessary to manage perioperative hypertension in cardiac surgery. At present, there are various types of drugs for hypertension control in clinical practice, and it is necessary to select vasoactive drugs suitable for cardiac surgery. Methods: A systematic search was conducted in PubMed (Medline), Embase, and the Cochrane Library databases to compare the safety of calcium channel blockers and other antihypertensive drugs in controlling hypertension during cardiac surgery, with the search ending in July 2024. For continuous variables, we utilized combined weighted mean difference (WMD) with a 95% confidence interval (CI) and risk ratio (RR) with a 95% confidence interval to assess both efficacy and safety. Results: A total of six randomized controlled trials were included, with a total of 1886 patients. There was no significant difference in mortality between calcium channel blockers and other vasodilators (RR=0.75, 95% CI: 0.45,1.26, P =0.28; I^2=0%, P=0.75). Also, there was no significant difference in the incidence of atrial fibrillation (RR=1.09, 95% CI: 0.94,1.26, P=0.26; I^2=13%, P=0.33). In addition, there were no significant differences in the incidence of myocardial infarction (RR=0.76, 95% CI: 0.41,1.39, P=0.37; I^2=0%, P=0.55) and renal insufficiency (RR=0.92, 95% CI: 0.65,1.31, P=0.66; I^2=40%, P=0.19) between the two groups. Finally, there was no significant difference in the incidence of total adverse events between the two groups (RR=1.05, 95% CI: 0.87,1.27, P=0.60; I^2=0%, P=0.68). Conclusion: Compared with other vasodilators, there is no significant difference in the safety of calcium channel blockers in controlling blood pressure in cardiac surgery.

Keywords: Calcium Channel Blockers; Heart Surgery; High Blood Pressure; Safety.

1. Introduction

With the advancement of medical technology, the annual global volume of patients undergoing cardiac surgery has reached 230 million [1]. Up to 80% of cardiac surgery patients and 25% of non-cardiac surgery patients experience acute hypertension during the perioperative period [2], emphasizing the critical importance of managing acute hypertension in the context of cardiac surgical procedures. Effective blood pressure control is a pivotal aspect of anesthesia for cardiac surgery [3, 4].

Pharmacological management options for perioperative hypertension include calcium channel blockers, nitroglycerin, nitrate pune, phentolamine, among others. Calcium channel blockers are drugs that inhibit the transmural flow of extracellular calcium through ion-specific channels. Two commonly used types exert differential effects on blood vessels and myocardial muscle. Dihydropyridines such as amlodipine and nicardipine primarily dilate arterial blood vessels to reduce blood pressure, while non-dihydropyridines like diltiazem and verapamil decrease heart rate and myocardial contractility while modestly dilating arterial blood vessels to lower blood pressure. Additionally, novel formulations of certain calcium channel blockers have been introduced into clinical practice [5, 6]. Nitroglycerin, a class of arteriovenous dilators, also has good efficacy in dilating coronary arteries. Nitrate pune exerts its vasodilatory effect by promoting NO production to widen blood vessels and reduce blood pressure. Each type of antihypertensive medication possesses distinct mechanisms, therapeutic effects, and adverse reactions; therefore comparative evaluation regarding efficacy and safety in the perioperative setting is warranted.

The meta-analysis of Yu Lin et al. suggested that the efficacy and tolerability of calcium channel blockers were better in the treatment of perioperative hypertension in patients undergoing non-cardiac surgery [7], but relevant studies on perioperative treatment of cardiac surgery are lacking. Against this backdrop, we undertook a systematic review encompassing randomized controlled trials and meta-analyses comparing the efficacy and safety profiles between calcium channel blockers versus other vasodilator therapies in addressing perioperative hypertension associated with cardiac surgeries.

2. Materials and Methods

2.1. Inclusion Criteria

2.1.1. Type of Research

Published or ongoing randomized controlled trials (RCTs).

2.1.2. The Objects of Studies

Heart surgery; older than 18 years; hypertension occurred before, during, or after surgery; calcium channel blockers, nitroglycerin, nitroprusside, and other vasodilators were used to lower blood pressure.

2.1.3. Types of Interventions

Any vasodilators (intravenous), mainly including calcium channel blockers such as clevidipine, nifedipine, and diltiazem, nitroglycerin, and nitroprusside.

2.1.4. Outcome Indicators

Number of deaths during treatment; The total number of adverse events; Number of myocardial infarctions; Number of episodes of atrial fibrillation; Number of cases of renal insufficiency. To compare whether there are differences in the safety of each vasodilator. Safety was the primary outcome indicator.

2.2. Exclusion Criteria

(1) non-randomized controlled trial (RCT); (2) non-Chinese and English literature; (3) non-adults; (4) non-cardiac surgery; (4) articles whose full text could not be obtained by contacting the author or other means, or whose data were missing or had errors; (5) Non-studies related to controlling blood pressure.

2.3. Search Strategy

2.3.1. Computer Search

The main databases searched were Medline (Pubmed), Cochrane Library, and Embase. In addition, we searched the clinical trial registration website ClinicalTrials.gov (http://clinicaltrials.gov) to retrieve unpublished or ongoing clinical trials. The search period was from database inception to July 2024 and was updated weekly. The search strategy mainly consisted of keywords plus free words. For example, the specific search strategy in Pubmed was shown in Box 1, and the search strategies in other databases were similar.

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#1 (((((((((((Cardiac Surgical Procedures[MeSH Terms]) OR (Procedure, Cardiac Surgical)) OR (Procedures, Cardiac Surgical)) OR (Surgical Procedure, Cardiac)) OR (Surgical Procedures, Cardiac)) OR (Surgical Procedures, Heart)) OR (Cardiac Surgical Procedure)) OR (Heart Surgical Procedures)) OR (Procedure, Heart Surgical)) OR (Procedures, Heart Surgical)) OR (SurgicalProcedure,Heart)) OR(Heart Surgical Procedure)
#2 ((((((((((((((((((((((((((((((Nitroglycerin[MeSH Terms]) OR (Glyceryl Trinitrate)) OR (Trinitrate, Glyceryl)) OR (Nitrolan)) OR (Nitrospan)) OR (Nitrostat)) OR (Perlinganit)) OR (Nitrong)) OR (Susadrin)) OR (Sustac)) OR (Sustak)) OR (Sustonit)) OR (Transderm Nitro)) OR (Nitroglyn)) OR (Trinitrin)) OR (Trinitrolong)) OR (Anginine)) OR (Dynamite)) OR (Gilustenon)) OR (Nitrangin)) OR (Nitro-Bid)) OR (Nitro Bid)) OR (NitroBid)) OR (Nitro-Dur)) OR (Nitro Dur)) OR (NitroDur)) OR (Nitrocard)) OR (Nitroderm)) OR (Nitroderm TTS)) OR (Nitrol)) OR (Tridil)
#3(((((((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])) OR (drug therapy[MeSH Subheading])) OR (randomly[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract])
#4 (animals[MeSH Terms]) NOT (humans[MeSH Terms])
#5 #3AND#4
#6 #1AND #2AND #5
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Box 1. Search strategy for Pubmed.

2.3.2. Manual Search

The references cited in the included articles and the references cited in relevant systematic reviews were searched through Web of Science or Pubmed. In addition, we searched relevant conference literature.

2.4. Literature Screening and Data Extraction

2.4.1. Literature Screening

Two authors of the systematic review (Xueming Chen, and Shiyan Chen) read and independently evaluated the titles and abstracts of the literature obtained from the database search to determine whether these studies met our inclusion criteria, and searched the full text of all potentially relevant literature. During the title, abstract, and full-text screening process, the two systematic review authors (Xueming Chen, and Shiyan Chen) made independent decisions on whether to include relevant studies, and disagreements were resolved through discussion. If a disagreement could not be resolved, the third author (Zecheng Yang) would discuss the matter with the above two authors and make the final decision on whether to include the study.

2.4.2. Data Extraction

Data extraction was conducted independently by two investigators (Xueming Chen, and Shiyan Chen), and the following information was extracted: the first author's name, year of publication, number of patients, age, geographic location, design of the included trial, intervention method, quality evaluation-related indicators, the primary outcome indicator, etc.

2.5. Risk of Bias Assessment of Included Studies

According to the Cochrane Handbook of Systematic Review of Interventions, the risk of bias was evaluated from seven perspectives, including random sequence generation, allocation concealment, blinding of participants and researchers, blinded measurement of outcomes, incomplete data on outcomes, selective reporting, and other biases. The quality bias risk assessment of the included literature was conducted using Review Manager 5.3.

2.6. Statistical Analysis

The statistical analysis was conducted using Review Manager 5.3. For dichotomous data, the risk ratio (RR) and 95% confidence interval (CI) were used for evaluation. For continuous variables, the weighted mean difference (WMD) and 95% CI were used for evaluation. The heterogeneity among included studies was analyzed using the $\chi 2$ test and I^2 value. When the significance level $\alpha < 0.05$ or I^2 value $> 50\%$, it was considered that the heterogeneity was significant. When the heterogeneity was not significant, a fixed-effects model was used for meta-analysis, and a random-effects model was used when the heterogeneity was significant, and the sources of heterogeneity were analyzed through sensitivity analysis and subgroup analysis. When the number of included literature was $\geqslant 10$, a funnel plot was used to evaluate whether there was publication bias. The significance level for meta-analysis was $\alpha=0.05$.

3. Results

3.1. Literature Screening Process and Results

A total of 1042 articles were obtained from three major databases and clinical trial registration websites (Pubmed: 533; Embase: 361; Cochrane Library: 138; Clinical trial registration websites: 0). Additionally, 10 articles were identified through manual search. After multiple steps of screening, six RCTs [8-13] were ultimately included. A total of 1,886 study participants were included, and the selection process and results were shown in Fig. 1.

3.2. Basic Characteristics of the Included Studies and Quality of the Risk of Bias Assessment Results

Six studies were included, with a total of 1866 participants, published between 1989 and 2014. Three studies included patients from the United States, one from the United Kingdom, one from Turkey, and one was a multicenter study from New Zealand and the United States. All six studies were RCTs, and the age of participants was mainly distributed between 58 and 66 years old. Specific basic information is shown in Table 1.

Quality bias risk assessment is shown in Fig. 2 and Fig. 3.

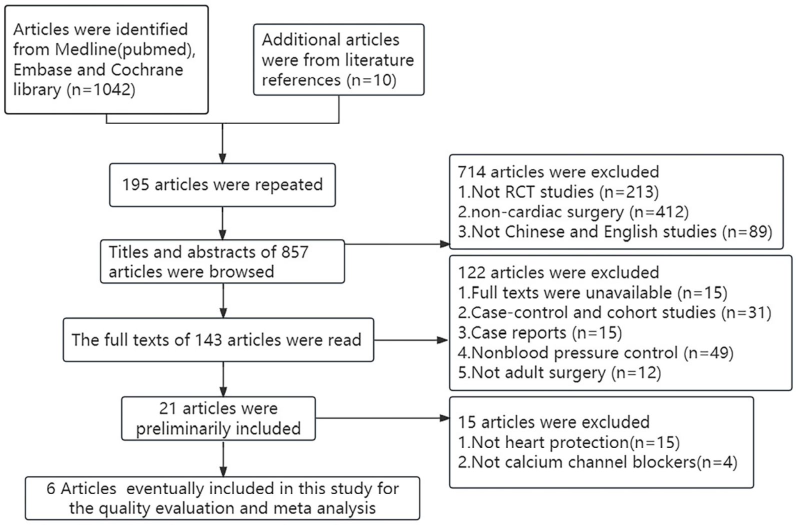

Figure 1. Flow chart of the literature selection process and results

Table 1. Basic characteristics of the included studies. CLV: Clevidipine; NTG: Nitroglycerin; SNP： Sodium Nitroprusside; NIC: Nicardipine.

Authors, years	intervention	type of Patients	Number	Country	Design	Age
Merry 2014	CLV/NTG	Coronary artery bypass grafting	100	New Zealand and USA	RCT	CLV 65.8 NTG 63.2
Aronson 2009	CLV/NTG/SNP/NIC	Heart surgery	1507	USA	RCT	CLV 64.5 NTG 63.9 SNP 65.3 NIC 66.1
Singla 2008	CLV/Placebo	Heart surgery	110	USA	RCT	CLV 63.8 Placebo 62.3
Levy 2007	CLV/Placebo	Heart surgery	104	USA	RCT	CLV 65.8 Placebo 61.7
Toraman 2005	CLV/NTG/SNP	Coronary artery bypass grafting	45	Turkey	RCT	CLV 58.0 NTG58.0 SNP58.0
Vecht 1989	NTG/NIC	Coronary artery bypass grafting	20	England	RCT	NTG 59 NIC 59

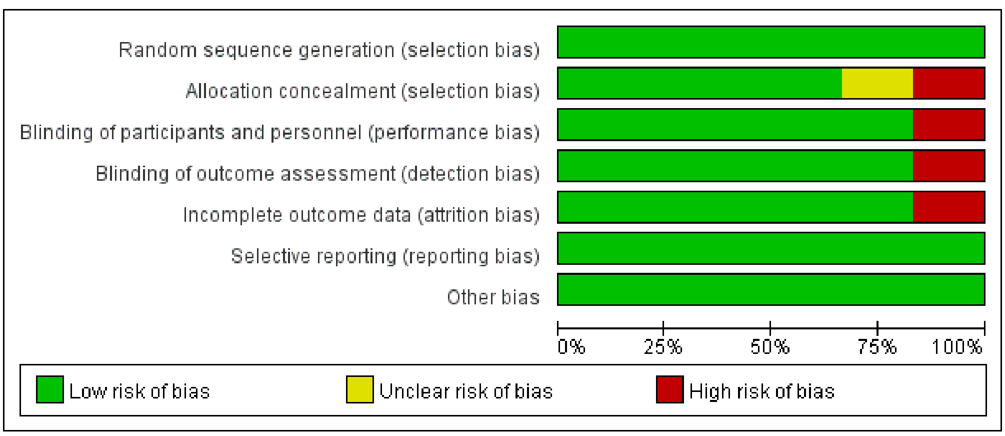

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

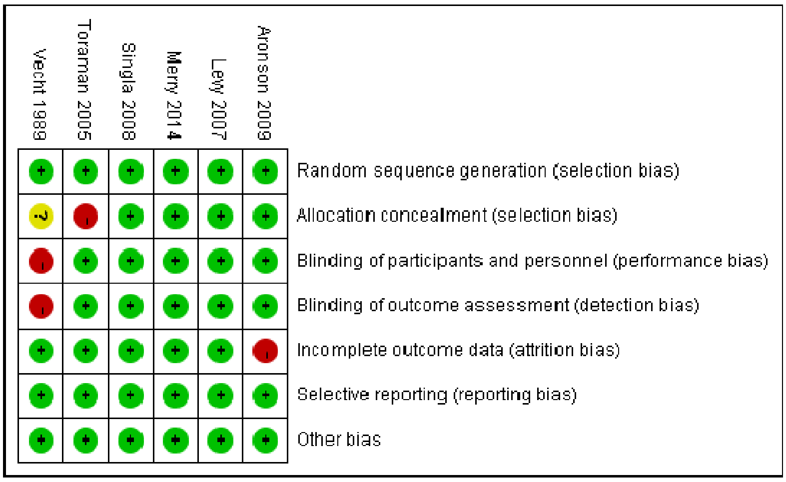

Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study

3.3. Meta-analysis Results

3.3.1. Mortality Rate

Six studies were included [1–6], with a total of 1886 participants. The I^2 value for heterogeneity test was 0%, indicating no obvious heterogeneity, so a fixed-effect model was used. According to the fixed-effect model meta-analysis, the mortality rate of calcium channel blockers was slightly higher than that of other vasodilators, but the difference was not statistically significant: RR=0.75, 95%CI (0.45, 1.26), P=0.28. See Fig. 4.

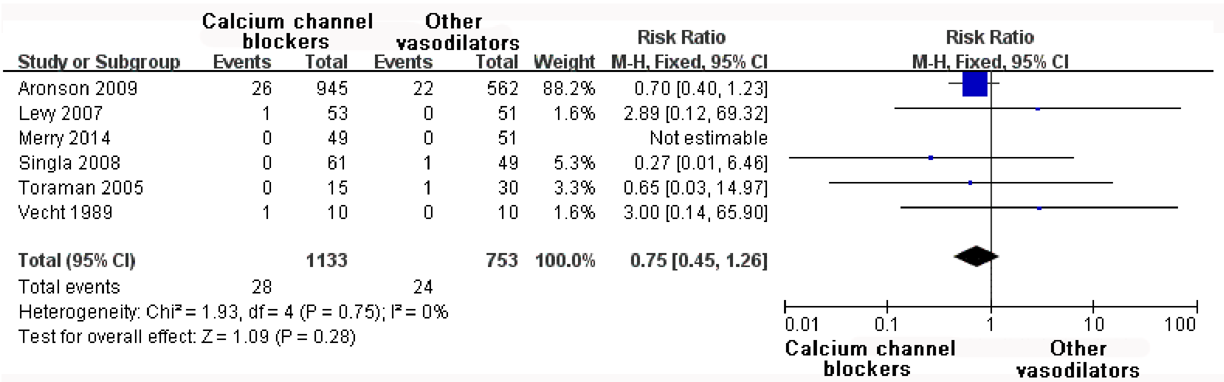

Figure 4. Meta-analysis of mortality rate in hypertension control with calcium channel blockers versus other vasodilators.

3.3.2. Incidence of Atrial Fibrillation

Four studies were included [1–4], with a total of 1820 participants. The I^2 value for heterogeneity test was 13%, indicating no obvious heterogeneity, so a fixed-effect model was used. According to the meta-analysis based on the fixed effects model, the incidence of atrial fibrillation for other vasodilators wsa slightly higher than that for calcium channel blockers, but the difference was not statistically significant: RR = 1.09, 95% CI (0.94, 1.26), P = 0.26. See Fig. 5.

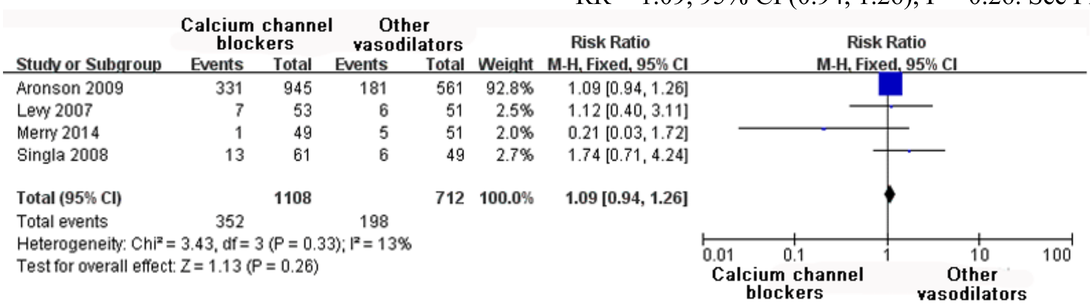

Figure 5. Meta-analysis of the incidence of atrial fibrillation in hypertension control with calcium channel blockers versus other vasodilators

3.3.3. Incidence of Myocardial Infarction

Four studies were included [1–4], with a total of 1820 patients. The I^2 value for heterogeneity was 0%, indicating that heterogeneity was not significant, so a fixed effects model was used. According to the meta-analysis based on the fixed effects model, there was no statistically significant difference between the two groups: RR = 0.76, 95% CI (0.41, 1.39), P = 0.37. See Fig. 6.

3.3.4. Incidence of Renal Insufficiency

Three studies were included [1–2, 4], with a total of 1711 patients. The I^2 value for heterogeneity was 40%, indicating that heterogeneity was not significant, so a fixed effects model was used. According to the meta-analysis based on the fixed effects model, the incidence of atrial fibrillation for calcium channel blockers was slightly higher than that for other vasodilators, but the difference was not statistically significant: RR = 0.92, 95% CI (0.65, 1.31), P = 0.66. See Fig.

7.

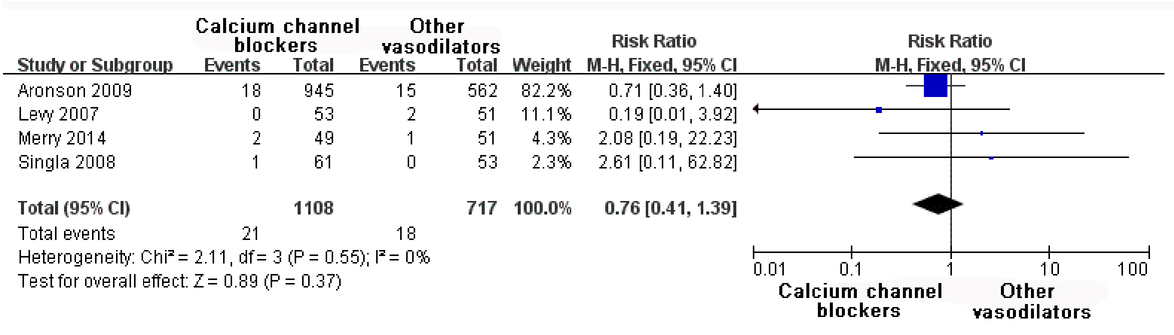

Figure 6. Meta-analysis of the incidence of myocardial infarction in hypertension control with calcium channel blockers versus other vasodilators

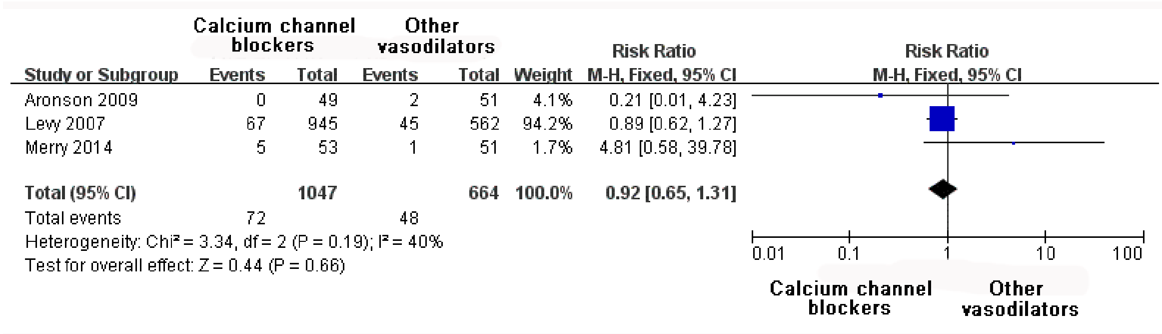

Figure 7. Meta-analysis of the incidence of renal insufficiency in hypertension control with calcium channel blockers versus other vasodilators.

3.3.5. Incidence of Total Adverse Events

Four studies [1-4] with 1820 patients were included. The I^2 value for heterogeneity was 0%, indicating that heterogeneity was not significant, so a fixed effects model was used. According to the meta-analysis based on the fixed effects model, the incidence of total adverse events for calcium channel blockers was slightly higher than that for other vasodilators, but the difference was not statistically significant: RR=1.05, 95% CI (0.87,1.27), P=0.60. See Fig. 8 for details.

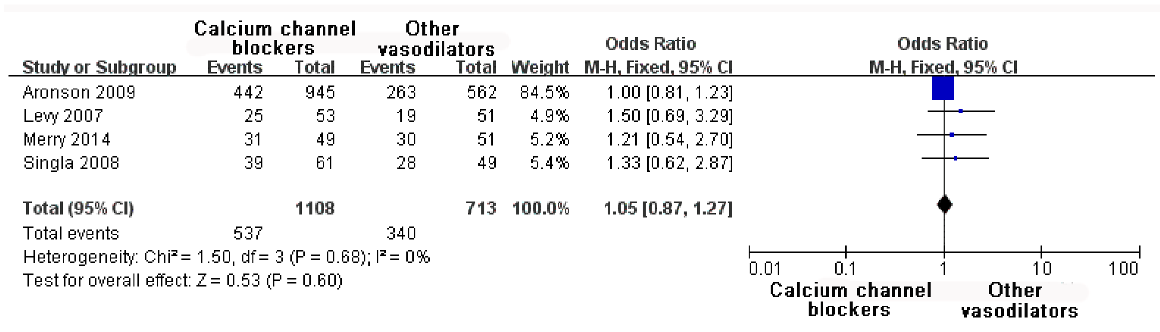

Figure 8. Meta-analysis of the incidence of total adverse events in hypertension control with calcium channel blockers versus other vasodilators

4. Discussion

This meta-analysis demonstrated no statistically significant difference in mortality, myocardial infarction, atrial fibrillation, renal dysfunction, and total adverse event rates between calcium channel blockers and other vasodilators, indicating equivalent safety profiles for calcium channel blockers and other vasodilators.

The results of our meta-analysis are consistent with those of the multicenter trial conducted by Aronson et al. [9], indicating that calcium channel blockers are safe and feasible for the treatment of acute hypertension in cardiac surgery. Among various adverse events, atrial fibrillation has the highest incidence, with an incidence of 31.8% in calcium channel blocker users and 27.8% in users of other vasodilators.

Nitroglycerin, nitroprusside, clevidipine, and diltiazem are commonly used to control blood pressure during cardiac surgery. However, each drug has its advantages and disadvantages. Nitroglycerin mildly expands the arterial system mainly by expanding the venous system, thereby reducing the preload on the heart and lowering blood pressure [14]. However, when the patient's blood volume is relatively insufficient, it may cause blood pooling in the venous system, which is not conducive to the stability of the patient's hemodynamics. In contrast, nitroprusside can cause more significant venous dilation than nitroglycerin, leading to marked reflex tachycardia [15], and the risk of cyanide poisoning is also higher [16]. Calcium channel blockers (CCB) inhibit the flow of calcium from the extracellular space by voltage-gated L-type calcium channels, and when calcium influx is suppressed, vascular smooth muscle cells relax, leading to vascular dilation and blood pressure reduction. At the same time, CCB also reduces the contractility of the heart muscle and slows the rate of sinus tachycardia and atrioventricular conduction [17]. Calcium channel blockers are divided into dihydropyridine (such as nifedipine and amlodipine) and non-dihydropyridine (such as diltiazem and verapamil) based on the different binding sites of CCB with L-type calcium channels [18].

There are some limitations in our study. This meta-analysis was planned to analyze the efficacy and safety of calcium channel blockers and nitroglycerin in controlling hypertension after cardiac surgery. However, the evaluation methods for efficacy in the included literature were quite different, and the data could not be effectively combined. In addition, the sample size of the studies on nitroglycerin was much smaller than that of calcium channel blockers, so to balance the differences in sample size, this study unified nitroglycerin, nitroprusside, and placebo as other vasodilators for research. Another limitation of this study is the restricted number of included studies and patient cases, necessitating further validation of data authenticity through large-scale randomized clinical trials (RCTs). Meanwhile, the studies included in this review were mostly conducted in Western countries, which may lead to regional differences. Additionally, due to language limitations, only Chinese and English literature could be read, and two studies were excluded [19; 20].

5. Conclusion

In summary, compared with other vasodilators, the safety difference in blood pressure control between calcium channel blockers and other vasodilators is not statistically significant. Calcium channel blockers can be safely used for blood flow management during cardiac surgery. Multi-center random clinical trials are still necessary to verify the efficacy and safety of different antihypertensive drugs in cardiac surgery. Clinical trials should focus on comparing the efficacy differences between different drugs.

Acknowledgments

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