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Effects of calcium channel blockers in patients with heart failure with preserved and mildly reduced ejection fraction: A systematic review and meta-analysis

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ABSTRACT

In contrast to beta-blockers and renin-angiotensin system inhibitors, the role of calcium channel blockers (CCBs) in patients with heart failure with preserved ejection fraction (HFpEF) remains uncertain. Despite several randomized controlled trials (RCTs) and cohort studies exploring the effects of CCBs on prognosis and exercise capacity in HFpEF patients, the findings have been inconsistent, likely due to limited statistical power and/or variations in study design. We aimed to conduct a systematic review and meta-analysis of studies on the effects of CCBs in HFpEF patients. The search of electronic databases identified 2 RCTs including 35 patients and 4 cohort studies including 25,078 patients. In cases of significant heterogeneity ($I^2 > 50$ %), data were pooled using a random-effects model; otherwise, a fixed-effects model was used. In pooled analysis of the cohort studies, use of CCBs was not associated with the risk of all-cause death (hazard ratio [95 % CI] = 0.913 [0.732, 1.139], $P_{random} = 0.420$) or hospitalization for heart failure (1.050 [0.970, 1.137], $P_{fix} = 0.230$). Separate analyses for dihydropyridine and non-dihydropyridine CCBs revealed similar results. In pooled analysis of the RCTs, verapamil increased exercise time (weighted mean difference [95 % CI] = 0.953 [0.109, 1.797] min; $P_{fix} = 0.027$) and decreased the congestive heart failure score (2.019 [1.673, 2.365] points; $P_{fix} < 0.001$) compared with placebo. In conclusion, in HFpEF patients, verapamil may improve exercise capacity and symptoms but use of CCBs, regardless of subclass, may not be associated with better prognosis. Our meta-analysis is limited by the inclusion of only several studies for each outcome and further research is necessary to confirm our findings.

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) is a substantial and growing clinical challenge, now accounting for nearly half of all heart failure cases in the community [1]. Despite the preserved ejection fraction (EF), HFpEF is associated with high rates of morbidity and mortality, similar to heart failure with reduced EF [2]. Managing HFpEF is particularly complex due to the diverse spectrum of clinical manifestations that patients experience [3]. While severe exercise intolerance is a common and debilitating symptom, patients may also present with symptoms such as dyspnea, fatigue, and fluid retention, all of which contribute to a significantly reduced quality of life [3]. The increasing prevalence of HFpEF, especially among elderly populations, highlights the urgent need for effective therapeutic strategies to manage this condition [1].

Sodium-glucose cotransporter 2 inhibitors are currently recommended as a class I indication for HFpEF patients [4]. While large, high-quality randomized controlled trials (RCTs) have explored the use of angiotensin receptor neprilysin inhibitors and mineralocorticoid receptor antagonists in HFpEF patients [5,6], current guidelines, including the 2023 Updated ESC Guidelines on Heart Failure, do not recommend these therapies for HFpEF due to the lack of conclusive evidence from clinical trials [4]. Non-dihydropyridine calcium channel blockers (CCBs) and beta-blockers are often considered first-line agents for heart rate control in HFpEF patients with atrial fibrillation in recent guidelines [7–9]. The 2021 ESC Guidelines for the Diagnosis and Treatment of

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Acute and Chronic Heart Failure further note the role of CCBs, not only for heart rate control but also for angina relief in HFpEF, though without a direct benefit on heart failure or coronary endpoints [7]. Due to the frequent coexistence of hypertension in HFpEF patients, the use of antihypertensive medications, including CCBs, is both recommended and common in their treatment [7,8,10]. While many cohort studies and several RCTs have examined the effectiveness of various antihypertensive drugs such as renin-angiotensin system (RAS) inhibitors and beta-blockers in HFpEF patients [11–16], the role of CCBs remains uncertain.

Despite several RCTs and cohort studies exploring the effects of CCBs on prognosis and exercise capacity in HFpEF, the findings have been inconsistent, likely due to limited statistical power and/or variations in study design [17–23]. Specifically, significant improvement in exercise capacity with CCB treatment was reported in one RCT [18], but in another RCT, such improvement was not observed [17]. An association between CCB use and better survival was observed in one cohort study [20], but in other cohort studies, such an association was not observed [19,21]. These discrepancies highlight gaps such as small sample sizes, differing patient populations, and variations in CCB subclasses used. Thus, there is a critical need to comprehensively synthesize existing evidence. Therefore, we aimed to conduct a systematic review and meta-analysis of studies on the effects of CCBs in these patients.

2. Methods

This study has been registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols with registration number of INPLASY202430097 (https://www.doi.org; https://doi.org/10.37766/inplasy2024.3.0097). This meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [24]. The protocol for this meta-analysis was published elsewhere [25].

2.1. Search strategy

Studies examining the effects of CCBs in HFpEF patients published until April 1, 2024 were identified using PubMed, Web of Science, and Scopus. For search of the eligible studies, the following keywords and Medical Subject Heading were used:

#1 “heart failure with preserved ejection fraction” OR “heart failure with normal ejection fraction” OR “diastolic heart failure”.

#2 “calcium channel blockers” OR “calcium channel antagonists”.

#3 “prognosis” OR “death” OR “mortality” OR “hospitalization” OR “outcomes”.

#4 “exercise capacity” OR “functional capacity” OR “exercise intolerance” OR “oxygen consumption” OR “oxygen uptake” OR “walk distance” OR “walk test” OR “quality of life”.

#5 #1 AND #2 AND #3 (primary outcome [prognosis]).

#6 #1 AND #2 AND #4 (secondary outcome [exercise capacity] and other outcomes [health-related quality of life and drug discontinuation due to adverse events such as bradycardia and hypotension).

Literature search was also conducted by manual screening of reference lists of relevant reviews and retrieved articles.

Two researchers (HF and TK) independently performed the literature search. We initially reviewed the titles and abstracts of each study, and if a study was considered relevant, we proceeded to read the full text. Disagreements were resolved by consensus.

2.2. Study design

RCTs and prospective and retrospective cohort studies were included. Case–control studies were excluded.

2.3. Selection criteria

Inclusion criteria for this meta-analysis were: (1) studies which included symptomatic heart failure patients with left ventricular (LV) EF≥40 % who were treated with CCBs; (2) comparison between CCBs and controls (placebo or standard medications); and (3) assessed prognosis, exercise capacity, quality of life, or adverse events such as bradycardia and hypotension. No restrictions were applied regarding the follow-up time of the patients. Only articles published in the English language were included.

2.4. Outcomes

The primary outcome of interest was prognosis, including all-cause death and hospitalization for heart failure. The secondary outcome of interest was exercise capacity assessed by peak oxygen uptake [26], 6-minute walk distance [27], or exercise time [28]. Other outcomes of interest were health-related quality of life assessed by the scores of the Minnesota Living With Heart Failure Questionnaire [29] and the Kansas City Cardiomyopathy Questionnaire [30], the congestive heart failure score [31], and drug discontinuation due to adverse events such as bradycardia and hypotension.

2.5. Data extraction

Two reviewers (HF and TK) independently extracted relevant data from retrieved studies, including author, study design, study time, country, number of participants, baseline characteristics, outcomes of interest, and information on the methodological quality. Disagreements were resolved by consensus.

2.6. Quality assessment

The quality of included RCTs was assessed using the Cochrane Risk of Bias tool [32]. The quality of included cohort studies was assessed using the revised and validated version of the Methodological Index for Non-Randomized Studies (MINORS) [33].

2.7. Statistical analysis

For mortality and morbidity, hazard ratios (HRs) controlling for confounding were pooled. For continuous outcomes, the effect size for the intervention was calculated by the difference between the means of the intervention and control groups at the end of the intervention. If the outcome was measured on the same scale, the weighted mean difference (WMD) and 95 % confidence interval (CI) were calculated. Otherwise, the standardized mean difference and 95 % CI were calculated. For each outcome, heterogeneity was assessed using the I^2 statistic; the $I^2 > 50$ % was considered significant. When there was significant heterogeneity, the data was pooled using a random-effects model; otherwise a fixed-effects model was used. For these analyses, Comprehensive Meta Analysis Software version 2 (Biostat, Englewood, NJ, USA) was used.

3. Results

3.1. Search results and characteristics

We initially screened 557 studies through our systematic search strategy. Based on the title and abstract review, 10 studies were selected for full-text review. The study by Wang et al. was excluded from our meta-analysis because it is an analysis of the TOPCAT trial [22]. The outcomes of the TOPCAT trial were included in our analysis through the study by Matsumoto et al. [23]. Consequently, a total of 2 RCTs including 35 patients and 4 cohort studies including 25,078 patients were included in the present meta-analysis. The study identification and selection process is summarized in Fig. 1.

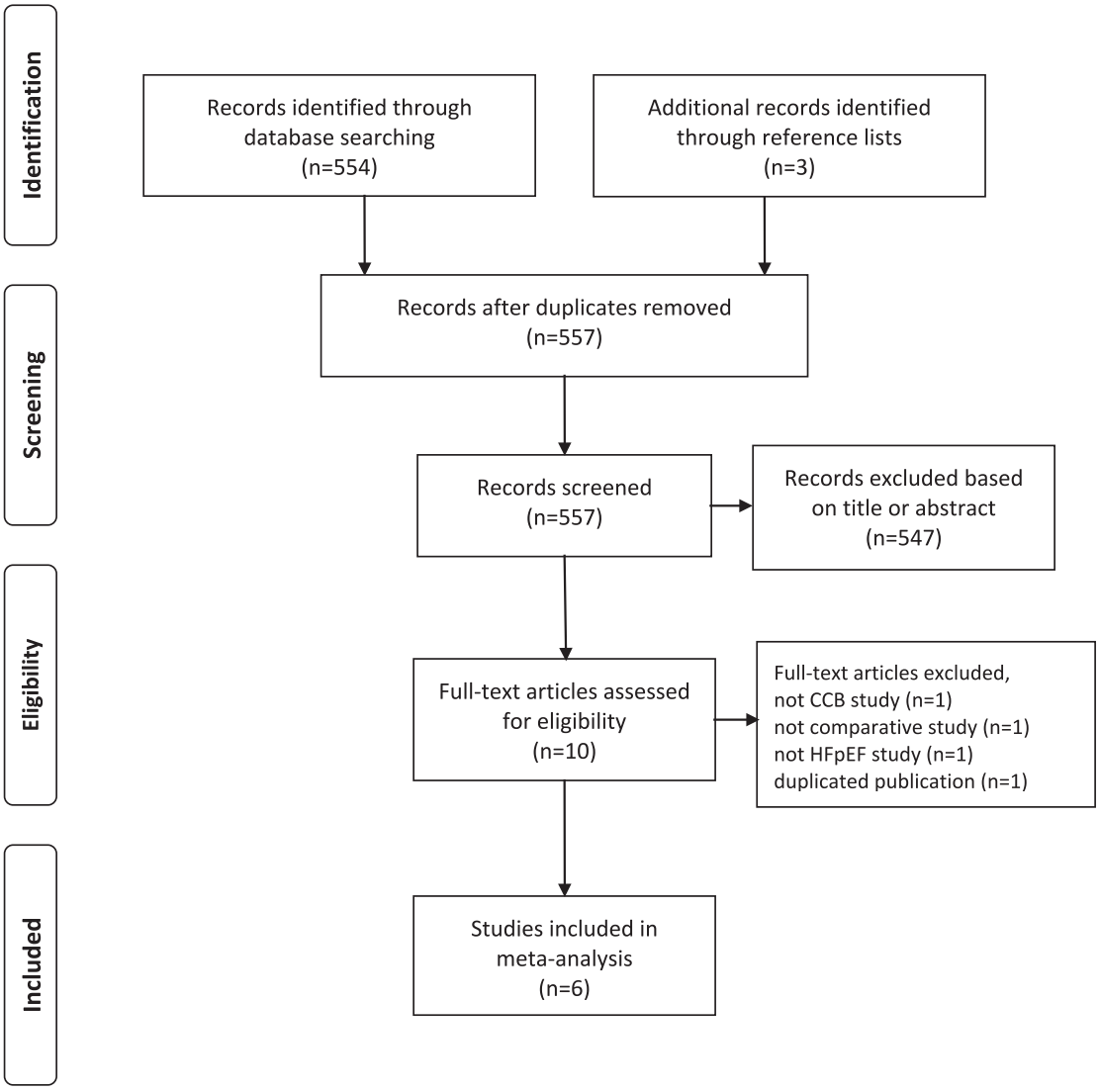

Fig. 1. Selection process for studies included in meta-analysis. CCB indicates calcium channel blockers; HFpEF, heart failure with preserved ejection fraction.

All the included RCTs used verapamil, a non-dihydropyridine CCB, and examined its effects on exercise capacity assessed by exercise time, quality of life assessed by the congestive heart failure score, and adverse events such as bradycardia and hypotension. All the included cohort studies examined the effect of CCBs on prognosis but did not assess exercise capacity, quality of life, or such adverse events. Two of these studies conducted separate analyses for dihydropyridine and non-dihydropyridine CCBs. Definition of preserved EF ranged from > 40 % to > 50 % across studies. The characteristics of the included studies are presented in Table 1.

The two RCTs included in this review received full scores on the Cochrane Risk of Bias tool, indicating a low risk of bias. However, it is important to note that both studies had relatively small sample sizes, which could limit the robustness of their findings. Additionally, one study exclusively included male patients [17], limiting the generalizability of its results. For the cohort studies, the MINORS scores ranged from 14 to 18 out of 24, reflecting a moderate risk of bias. Common issues identified included potential selection bias, confounding factors, and the retrospective nature of some studies. These biases influence the reliability and applicability of the findings. The risk of bias summary for RCTs and cohort studies is presented in **Supplemental Fig. 1** and **Supplemental Table 1**, respectively.

The mean age across the included studies ranged from 65 to 81 years. The proportion of male participants varied, ranging from 37 % to 100 %. The mean LVEF ranged from 56 % to 70 %. The patient characteristics of the included studies are presented in Table 2.

3.2. Primary outcome

Use of CCBs was not associated with the risk of all-cause death (HR [95 % CI] = 0.913 [0.732, 1.139], $P_{random} = 0.420$; $I^2 = 77.7$ %; Fig. 2A). Separate analyses for dihydropyridine and non-dihydropyridine CCBs revealed similar results; use of dihydropyridine or non-dihydropyridine CCBs was not associated with the risk of all-cause death (HR [95 % CI] = 0.988 [0.899, 1.085], $P_{random} = 0.794$; $I^2 = 51.3$ % for dihydropyridine CCBs; Fig. 2B and 1.050 [0.849, 1.299], $P_{random} = 0.651$; $I^2 = 55$ % for non-dihydropyridine CCBs; Fig. 2C).

Use of CCBs was not associated with the risk of hospitalization for heart failure (HR [95 % CI] = 1.050 [0.970, 1.137], $P_{fix} = 0.230$; $I^2 = 0$ %; Fig. 3A). Separate analyses for dihydropyridine and non-dihydropyridine CCBs revealed similar results; use of dihydropyridine CCBs or non-dihydropyridine CCBs was not associated with the risk of hospitalization for heart failure (HR [95 % CI] = 1.068 [0.970, 1.176], $P_{fix} = 0.182$; $I^2 = 0$ % for dihydropyridine CCBs; Fig. 3B and 1.042 [0.905, 1.199], $P_{fix} = 0.570$; $I^2 = 0$ % for non-dihydropyridine CCBs; Fig. 3C).

Table 1
Study characteristics.

Study	Design	Country	Major inclusion criteria	No. of patients, CCBs/non-CCBs	Intervention or follow-up period	End points	Type of CCBs	Method to control for confounding
Setaro 1990 [17]	Randomized placebo-controlled crossover	USA	Symptomatic HF, LVEF>45 % and abnormal diastolic filling by radionuclide angiography	20/20	2 weeks	Exercise time, CHF score, Adverse events	Verapamil	None
Hung 2002 [18]	Randomized placebo-controlled crossover	Taiwan	Symptomatic HF, NYHA class II-III, LVEF>50 % and evidence of LV diastolic dysfunction by echocardiography	15/15	3 months	Exercise time, CHF score, Adverse events	Verapamil	None
Fukuta 2005 [19]	Prospective cohort study	USA	Symptomatic HF, NYHA class ≥II, LVEF≥50 % by echocardiography	37/100	2 years	All-cause death	Not reported	Multivariate analysis
Wu 2014 [20]	Prospective cohort study	Taiwan	Symptomatic HF, NYHA class II-III, LVEF≥50 % and evidence of LV diastolic dysfunction by echocardiography	210/228	12 years	All-cause death	Not reported	Multivariate analysis
Patel 2014 [21]	Prospective cohort study	USA	Discharge diagnosis of HF based on ICD-9-CM codes, LVEF≥40 %	815/6699	6 years	All-cause death, Hospitalization for HF	DHP (amlodipine) and non-DHP CCBs	Propensity score analysis
Matsumoto 2023 [23]	Retrospective analysis of 4 HFpEF trials*	International	Symptomatic HF, NYHA class II-IV, LVEF≥40 % or ≥ 45 % and evidence of structural heart disease by echocardiography and/or elevated BNP levels	5874/11080	34.1 month (median)	All-cause death, Hospitalization for HF	DHP and non-DHP CCBs	Propensity score analysis

BNP indicates B-type natriuretic peptide; CCBs, calcium channel blockers; CHF, congestive heart failure score; DHP, dihydropyridine; HFpEF, heart failure with preserved ejection fraction. ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

* HFpEF trials included the I-Preserve, the TOPCAT, the PARAGON-HF, and the DELIVER trials.

Table 2
Patient characteristics.

Study	EF (mean ± SD), %	Age (mean ± SD), years	Male	Hypertension	Diabetes	CAD	AF	ACE-I or ARB	Beta-blockers	Diuretics
Setaro 1990 [17]	60 ± 9	68 ± 5	100 %	75 %	35 %	25 %	0 %	0 %	0 %	85 %
Hung 2002 [18]	70 ± 9	65 ± 7	60 %	47 %	Not reported	0 %	0 %	Not reported	Not reported	Not Reported
Fukuta 2005 [19]	62 ± 7	65 ± 14	43 %	80 %	23 %	58 %	Not reported	55 %	50 %	50 %
Wu 2014 [20]	67 ± 9	65 ± 9	54 %	63 %	28 %	11 % *	16 %	35 %	43 %	69 %
Patel 2014 [21]	56 ± 9	81 ± 8	37 %	76 %	38 %	45 %	37 %	45 % †	57 %	80 %
Matsumoto 2023 [23]	57 ± 9	72 ± 9	51 %	91 %	40 %	24 % *	47 %	86 %	76 %	70 %

ACE-I indicates angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CAD, coronary artery disease; EF, ejection fraction.

* The value is presented as a proportion of patients who had prior myocardial infarction.

† The value is presented as a proportion of the use of ACE-I.

3.3. Secondary and other outcomes

Verapamil increased exercise time compared with placebo (WMD [95 % CI] = 0.953 [0.109, 1.797] min; $P_{fix} = 0.027$; $I^2 = 0$ %; Fig. 4A). Verapamil decreased congestive heart failure score compared with placebo (WMD [95 % CI] = 2.019 [1.673, 2.365] points; $P_{fix} < 0.001$; $I^2 = 0$ %; Fig. 4B). Although minor adverse events of verapamil, such as mild constipation, were noted, no discontinuation of verapamil due to adverse effects like bradycardia or hypotension was reported.

4. Discussion

In the present meta-analysis, the use of CCBs, regardless of class, was not associated with better prognosis in HFpEF patients. Verapamil, a non-dihydropyridine CCB, improved exercise capacity and symptoms in HFpEF patients. No major adverse effects were reported with the use of verapamil in HFpEF patients.

In contrast to our meta-analysis, one previous meta-analysis of 2 RCTs and 3 cohort studies including 11,208 patients reported the potential benefits of CCBs for all-cause mortality and hospitalization [34]. However, we consider this meta-analysis limited for several reasons. First, the analysis failed to stratify between dihydropyridine and non-dihydropyridine CCBs, despite their distinct pharmacological profiles; dihydropyridine CCBs tend to be more potent vasodilators than non-dihydropyridine CCBs, whereas the latter have more marked negative inotropic effects [35]. Second, the meta-analysis overlooked multiple RCTs and cohort studies pertinent to the topic [17–20]. Additionally, the meta-analysis included a study of non-HFpEF patients [36]. Finally, a

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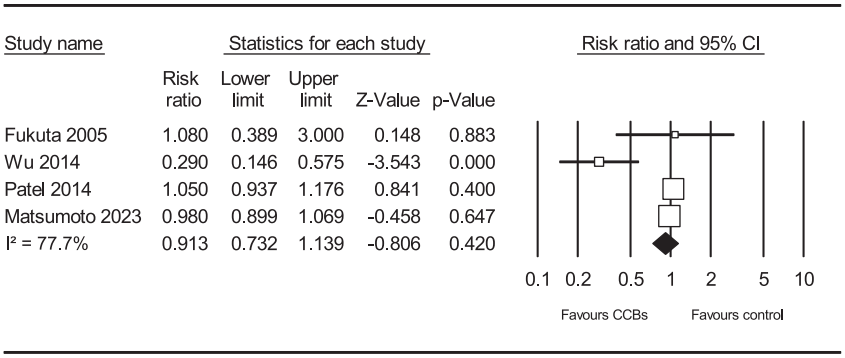

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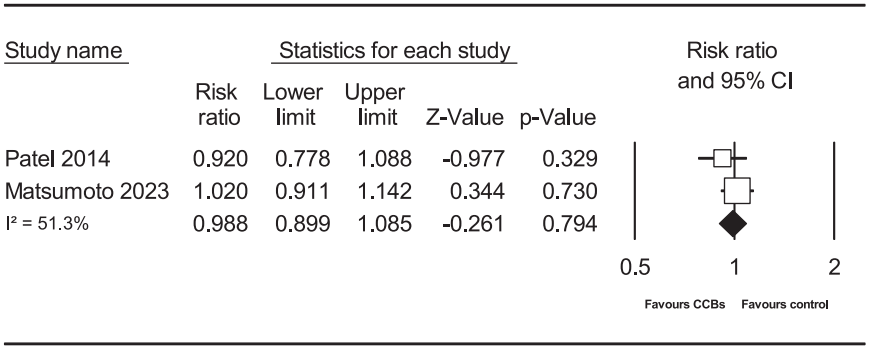

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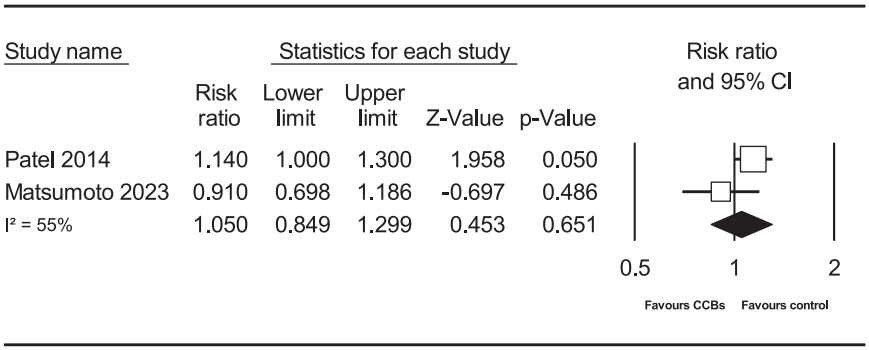

Fig. 2. Forest plots showing the effects of calcium channel blockers (CCBs; A), dihydropyridine CCBs (B), and non-dihydropyridine CCBs (C) on all-cause death.

significant observational analysis of pooled data from large HFpEF trials, including the I-Preserve, TOPCAT, PARAGON-HF, and DELIVER trials, has been published since the completion of the meta-analysis [23] and it is inconsistent with the meta-analysis [34].

In our meta-analysis, verapamil, a non-dihydropyridine CCB, improved exercise capacity and symptoms without major adverse effects in HFpEF patients. While our meta-analysis does not elucidate the precise mechanisms underlying the observed exercise benefit of verapamil in HFpEF patients, several plausible explanations exist. One reason is that verapamil has been reported to decrease LV end-diastolic pressure and to improve isovolumic relaxation time in HFpEF patients [18]. Given that increased left atrial pressure is one of the mechanisms for

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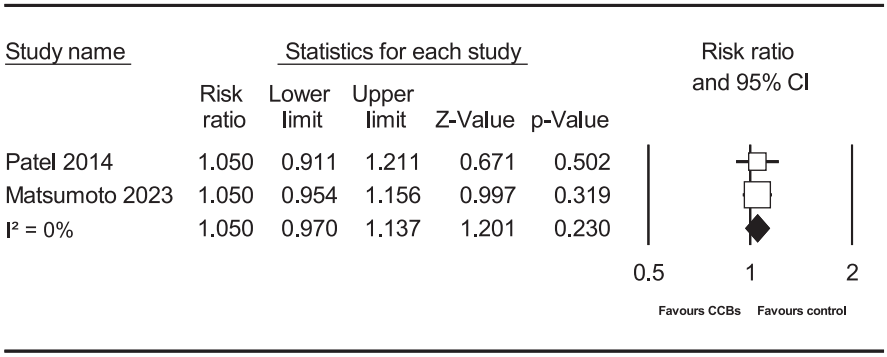

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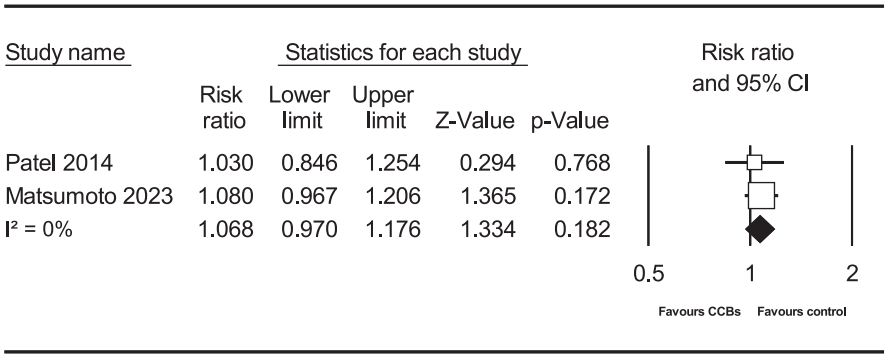

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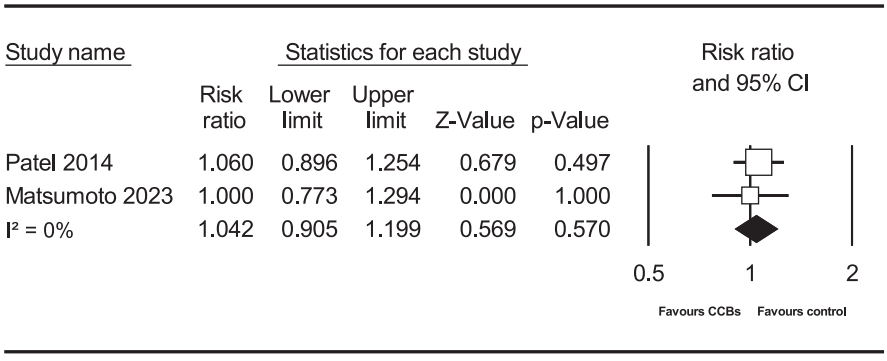

Fig. 3. Forest plots showing the effects of calcium channel blockers (CCBs; A), dihydropyridine CCBs (B), and non-dihydropyridine CCBs (C) on hospitalization for heart failure.

exertional dyspnea in HFpEF patients [37], the observed improvement in exercise capacity with verapamil may partly result from the reduction of left atrial pressure during exercise. Additionally, improved LV relaxation with verapamil could contribute to reducing left atrial pressure by enhancing LV filling during exercise.

While our meta-analysis suggests that verapamil may improve exercise capacity and symptoms in patients with HFpEF, it is important to consider recent evidence that links lower heart rates with worse outcomes in this patient population [38,39]. HFpEF is often associated with chronotropic incompetence, where the heart's ability to increase its rate

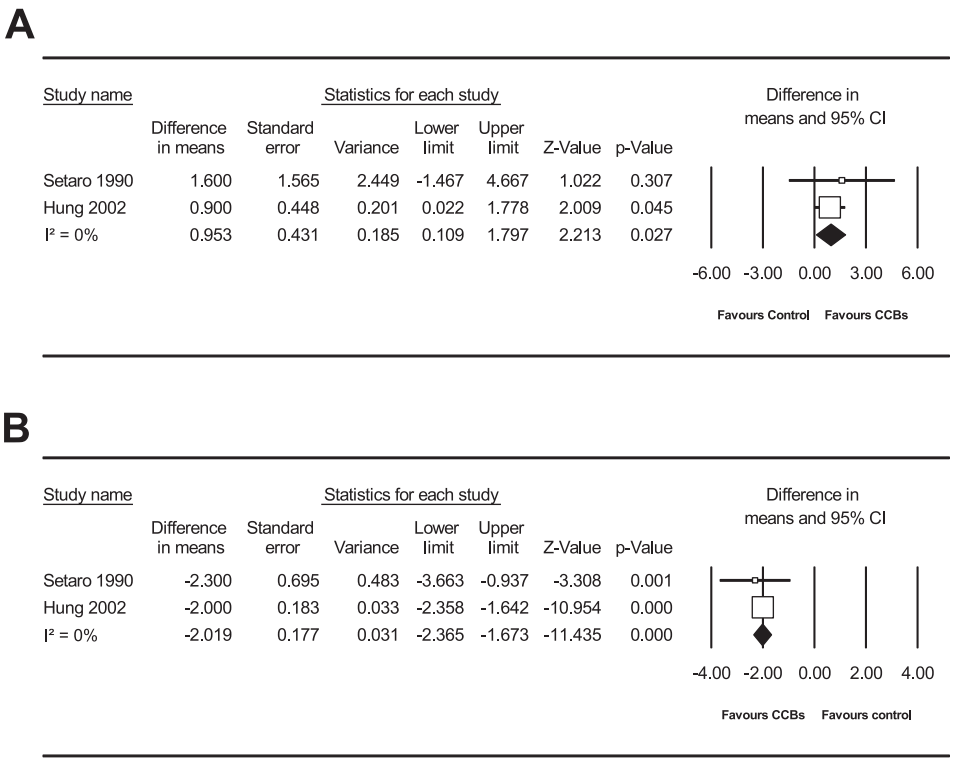

Fig. 4. Forest plots showing the effects of verapamil on exercise time (min; A) and the congestive heart failure score (points; B) (exercise capacity and symptom).

during physical activity is impaired [3]. This chronotropic incompetence may already limit exercise tolerance and overall cardiovascular function in HFpEF patients. The use of heart rate-lowering medications, such as non-dihydropyridine CCBs, could potentially exacerbate these issues by further reducing heart rate, leading to insufficient cardiac output to meet tissue's demands. This might partially explain why our meta-analysis did not find an association between non-dihydropyridine CCB use and improved prognosis, despite observed benefits in exercise capacity and symptom relief.

There are several limitations to the present study. First, the limited number of studies included in our meta-analysis and inconsistencies in the reporting of outcomes of interest resulted in a meta-analysis with only several studies for each outcome. Our findings demonstrated statistical significance when all included studies individually yielded significant findings, yet failed to achieve significance when these studies did not. This highlights a limitation of our study and emphasizes the need for caution in interpreting our findings.

Second, several studies included in our meta-analysis defined preserved EF as greater than or equal to 40 % or 45 % [17,21,23], which is inconsistent with the guidelines' definition of HFpEF [7,8]. However, most of the included patients appeared to have EF≥50 % (Table 2). Additionally, patients with heart failure and EF of 40 % to 50 % exhibit similar clinical and prognostic characteristics to those with EF>50 % [40].

Third, the observed neutral effects of CCBs on prognosis are derived from cohort studies. The moderate MINORS scores (14–18 out of 24) for the cohort studies highlight several methodological limitations, including selection bias and confounding factors, which could affect the overall findings of our meta-analysis. These biases underscore the need for cautious interpretation of the findings. While conducting traditional RCTs is not practical and may raise ethical concerns, new well-designed studies such as registry-based RCTs are warranted.

Finally, although the observed exercise benefit of verapamil in HFpEF patients is derived from well-conducted RCTs, the small number of participants, short-term follow-up, crossover study design, and the inclusion of only male patients in one study impact the generalizability and strength of the evidence. Furthermore, it should be noted that the trials of verapamil were conducted in a highly selected patient group, excluding patients with coronary artery disease or atrial fibrillation, which are common in HFpEF patients (Table 2) [17,18]. Additionally, these trials were conducted several decades ago, and the concomitant medications, such as RAS inhibitors or beta-blockers, differed from those currently used (Table 2). Therefore, the observed exercise benefit of verapamil should be re-evaluated in larger, more diverse, and contemporary populations with long-term follow-up.

5. Conclusion

In our meta-analysis, the use of CCBs, regardless of subclass, was not associated with improved survival in HFpEF patients. However, the observed neutral effects of CCBs on prognosis are derived from cohort studies. The moderate risk of bias in the cohort studies underscores several methodological limitations, including selection bias and confounding factors, which highlights the need for cautious interpretation of the findings. Although the observed exercise benefit of verapamil in HFpEF patients is derived from well-conducted RCTs, the small number of participants, short-term follow-up, crossover study design, and the inclusion of highly selected patients impact the generalizability and strength of the evidence.

- Systematic review registration

  INPLASY202430097.

CRediT authorship contribution statement

Hidekatsu Fukuta: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Toshihiko Goto:** Writing – review & editing, Conceptualization. **Takeshi Kamiya:** Writing – review & editing, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101515.

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