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REVIEW

Bromocriptine in peripartum cardiomyopathy: A meta-analysis with trial sequential analysis

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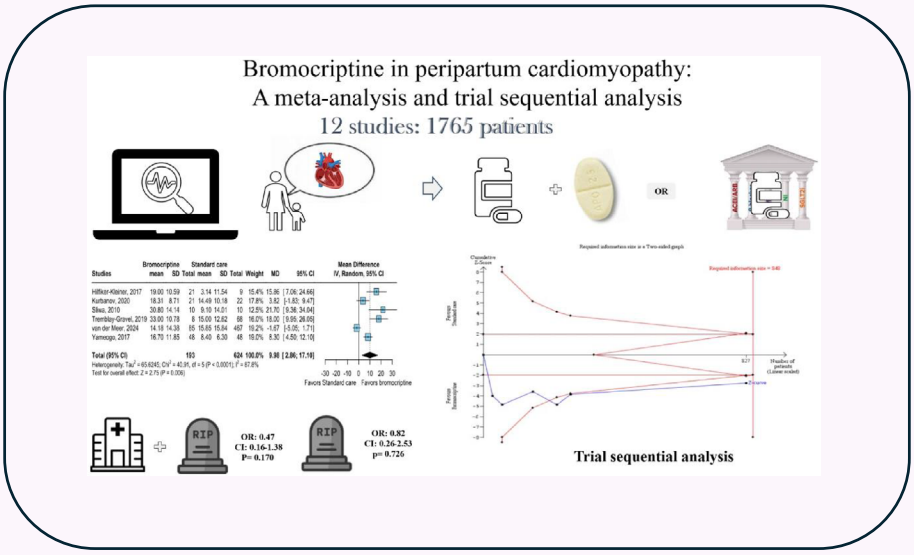
Abstract

Bromocriptine has been proposed as a disease-modifying therapy for peripartum cardiomyopathy (PPCM). The long-term outcomes of bromocriptine use remain uncertain. We conducted a systematic review, meta-analysis and trial sequential analysis (TSA) to assess the long-term efficacy and safety of bromocriptine in combination with standard care versus standard care alone in patients with PPCM. We systematically searched PubMed, Embase and Cochrane up until March 2025 for published studies comparing bromocriptine plus standard care with standard care alone in patients with PPCM. The outcomes included changes in left ventricular (LV) ejection fraction, LV end-systolic and end-diastolic dimensions, major adverse cardiovascular events (MACE), all-cause mortality and rehospitalization. We computed mean differences (MDs) for continuous outcomes and odds ratios (ORs) for binary endpoints with 95% confidence intervals (CIs). We used TSA to assess the conclusiveness of the available evidence. A total of 12 studies [2 randomized controlled trials (RCTs) and 10 observational studies] and 1765 patients (age range 29–33.8 years) were included, of whom 474 (26.9%) received bromocriptine with standard care and 1291 (73.1%) received standard care alone. Compared with standard care alone, bromocriptine with standard care was associated with a significant improvement in LV ejection fraction (MD 9.98%; 95% CI: 2.86 to 17.10; $P < 0.001$), LV end-diastolic diameter (MD −2.51 cm; 95% CI: −4.23 to −0.79; $P = 0.004$), and LV end-systolic diameter (MD −5.61 cm; 95% CI: −10.03 to −1.18; $P = 0.010$). The proportion of patients with improved LV function was higher in those who received bromocriptine with standard care than in those who received standard care alone (OR 0.35; 95% CI: 0.16 to 0.75; $P = 0.007$). There were no significant differences between groups regarding the incidence of MACE, all-cause mortality or heart failure rehospitalization. The TSA showed that LV ejection fraction and diastolic dimension reached the required information size (RIS); however, only LV ejection fraction crossed the monitoring boundary before the full sample size was achieved. In this meta-analysis with TSA, the use of bromocriptine with standard care was associated with improved LV function and remodelling in patients with PPCM compared with standard care alone, with a similar effect on mortality and re-hospitalization. TSA indicated that current evidence is promising, but larger and adequately powered randomized trials are needed to confirm bromocriptine's cardioprotective effects.

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Graphical Abstract

In this meta-analysis of 12 studies (1,765 patients), adjunctive bromocriptine significantly improved left ventricular ejection fraction and remodeling in peripartum cardiomyopathy without improving mortality or major adverse cardiovascular events. Trial sequential analysis indicated that current evidence is suggestive but not yet conclusive, underscoring the need for larger randomized trials to confirm its potential cardioprotective role.



Keywords bromocriptine; long-term outcomes; peripartum cardiomyopathy; standard of care; trial sequential analysis

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Introduction

Peripartum cardiomyopathy (PPCM) is a potentially life-threatening cause of heart failure defined by new-onset left ventricular (LV) systolic dysfunction in late pregnancy or within 5 months postpartum, without another identifiable cause of cardiac disease.[1,2] It remains a major contributor to pregnancy-associated morbidity and mortality.[3] Recent pathophysiological evidence has implicated a cleaved 16-kDa prolactin fragment with anti-angiogenic and pro-apoptotic effects that may drive myocardial injury and adverse remodelling.[4,5]

Bromocriptine, a dopamine D_2 receptor agonist that suppresses prolactin secretion, has therefore been investigated as a potential disease-modifying therapy for PPCM. Randomized trials, observational studies and meta-analytic findings suggest possible LV remodelling and recovery and improvements in clinical outcomes with the use of bromocriptine in patients with PPCM, but findings have been inconsistent.[6–13] Prior meta-analyses focused mainly on short-term outcomes, limited to the assessment of regional variations, and did not incorporate trial sequential analysis (TSA), leaving uncertain the long-term durability of treatment effects of bromocriptine.[11–13] Consequently, the European Society of Cardiology (ESC) guidelines have given a class IIb recommendation for bromocriptine use in patients with PPCM.[14]

Therefore, we conducted a systematic review and meta-analysis evaluating the use of bromocriptine in addition to standard therapy versus standard care alone in PPCM.

Methods

Protocol and registration

This systematic review and meta-analysis was designed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[15] This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under protocol number CRD420251004225.

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Search strategy and data extraction

MEDLINE, Embase and Cochrane databases were systematically searched from inception to 20 March 2025. The search strategy employed in PubMed was: ('Peripartum cardiomyopathy' OR 'Peripartum cardiomyopathy'[Mesh] OR 'postpartum cardiomyopathy' OR 'pregnancy-associated cardiomyopathy' OR 'pregnancy-related cardiomyopathy' OR 'pregnancy-induced heart failure' OR 'maternal heart failure' OR 'cardiac dysfunction during pregnancy' OR PPCM) AND (Bromocriptine OR 'bromocriptine mesylate' OR 'Bromocriptine'[Mesh] OR Parlodel OR Cycloset OR '2-Bromo-alpha-ergocryptine' OR 'dopamine agonist' OR 'ergot derivative'). In addition, we evaluated the references of included studies and previous reviews for additional studies. Two authors (U.G.A. and N.T.) independently performed the search and extracted the data based on pre-defined criteria. The full search strategy in all the databases is provided in Table S1. Disagreements were resolved by consensus between the authors. The data extraction from eligible studies was independently conducted by two investigators (U.G.A. and N.T.) using a standardized data extraction sheet. Extracted data included study design, country, total participants, age, follow-up duration, parity, functional class defined by New York Heart Association (NYHA), definition criteria of PPCM and outcomes.

Eligibility criteria

We included studies that met the following inclusion criteria: (1) randomized controlled trials (RCTs) or observational studies, (2) recruited patients with PPCM, (3) compared bromocriptine plus standard care versus standard care alone, and (4) had a median follow-up duration of $\geq$6 months. We excluded studies with (1) no clinical outcomes of interest, (2) including other forms of heart failure, (3) overlapping studies and (4) previous meta-analyses, editorials, case reports or studies that did not use bromocriptine. In cases of overlapping patient populations, we included the most recent study that reported the largest number of relevant outcomes.

Endpoints and subgroup analyses

The endpoints of interest were major adverse cardiovascular events (MACE), all-cause mortality, rehospitalization, mean change in LV function, persistent LV dysfunction and LV dimensions in systole and diastole. Due to the variations in the definitions of key outcomes, including MACE and LV recovery, we adopted study-reported outcome definitions along with details of the standardization applied in the pooled analysis (Table S2). We performed subgroup analyses of (1) data from RCTs and observational studies, (2) baseline LV ejection fraction and (3) duration of follow-up.

Quality assessment

Randomized controlled trials (RCTs) were evaluated using the Cochrane Risk-of-Bias tool (RoB 2), which assesses five domains: selection, performance, detection, attrition and reporting and classifies studies as 'low risk,' 'some concerns,' or 'high risk.'[16] Observational studies were assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool.[17] Two authors (U.G.A. and N.T.) independently assessed the risk of bias for all included studies. Any disagreements between the reviewers were resolved through discussion and consensus. Publication bias was assessed with funnel-plot analysis of endpoints to evaluate the symmetrical distribution of trials with similar weights. Egger's regression test was applied to quantify potential bias.

Statistical analysis

Treatment effects for continuous outcomes were compared using mean differences (MDs), whereas binary endpoints were pooled using odds ratios (ORs) with 95% confidence intervals (CIs). We applied the Mantel–Haenszel test in all binary endpoints and the inverse variance for continuous outcomes. Heterogeneity was examined with Cochran's Q test, Higgin's I^2 statistics and T^2 using the restricted maximum likelihood estimator. Heterogeneity was reported as low (I^2 = 0–25%), moderate (I^2 = 26–50%), or high ($I^2 > 50\%$). The DerSimonian and Laird random effects model was used for all analyses.

A leave-one-out analysis was performed to explore the source of heterogeneity when heterogeneity $I^2 > 50\%$. Meta-regression was conducted to examine the relationship between mean change in LV ejection fraction and LV diastolic dimension, along with the covariates of study design and baseline LV ejection fraction.

We performed TSA (program version 0·9.5·10 beta) for five key outcomes: LV recovery, persistent LV dysfunction, MACE and mean change in LV diastolic dimension and ejection fraction. We quantified trial sequential monitoring boundaries (TSMB) and required information size (RIS), adjusting for diversity based on an overall type I error of 5% and 80% statistical power. All analyses followed the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.[16] P-values < 0.05 were considered statistically significant for treatment effects. All statistical analyses were performed using R statistical software, version 4.2.2 (R Foundation for Statistical Computing) and the RevMan version 5.4.1 for statistical analysis (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

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Protocol changes

The following modifications were made to our registered PROSPERO protocol. We modified the aim to include long-term effects and safety of bromocriptine in combination with standard care and standard care in patients with PPCM. We also conducted TSA because most of the included studies allocated fewer patients to the bromocriptine with standard care group to further increase the robustness of our conclusion. All included studies administered bromocriptine in addition to standard heart failure therapy. Comparisons were therefore between bromocriptine and standard care versus standard care alone, or between different bromocriptine dosing regimens or durations on top of standard therapy. No study evaluated bromocriptine as monotherapy.

Results

Study selection and baseline characteristics

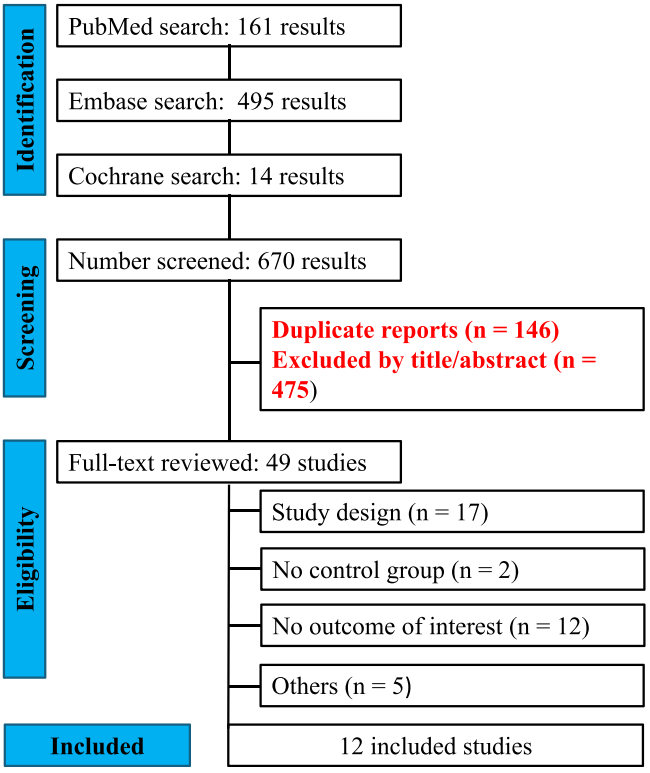
Our systematic search yielded 670 results (*Figure 1*). After removing duplicates, 49 studies remained for full review. Of these, 2 RCTs[6,7] and 10 non-RCT studies[8,9,18–25] were included in our analysis. We included a total of 1765 participants, of whom 474 participants (26.9%) were assigned to bromocriptine in addition to standard guideline-directed medical therapy. Studies were conducted across Europe, Africa and Asia, with publication years ranging from 2010 to 2023. The mean age of patients ranged from 28 to 33 years, and baseline LVEF ranged between 23% and 32%. The duration of follow-up varied considerably, from 6 to 76 months. Most patients received background GDMT, although the use of anticoagulation and device therapy was inconsistently reported across studies. Detailed study characteristics are provided in *Table 1*.

Pooled analysis of all studies

Mean change in LV ejection fraction

The mean change in LV ejection fraction was reported in 6 studies, two RCTs[6,7] and four observational studies.[9,20,22,25] Compared with the standard care, bromocriptine plus standard care was associated with a higher improvement in LV ejection fraction (MD 9.98%; 95% CI: 2.86 to 17.10; $P < 0.001$; $I^2 = 87.8\%$; *Figure 2A*). Subgroup analysis showed

Figure 1 PRISMA flow diagram of study screening and selection. The search strategy in PubMed, Embase, and Cochrane yielded 670 studies, of which 49 were fully reviewed based on pre-specified eligibility criteria. Twelve studies were included in the meta-analysis. PRISMA, preferred reporting items for systematic reviews and meta-analysis.



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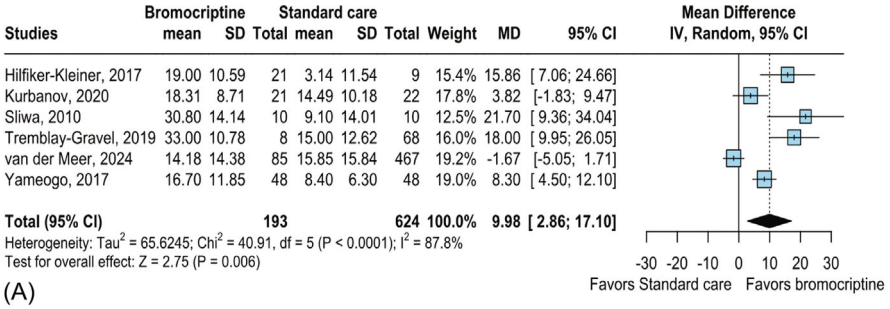
Table 1 Baseline characteristics of included studies

Study	Study design	Sites/countries	Number of patients, I/C	Age, years (mean or median), I/C	Parity I/C	Baseline LVEF (%) I/C	Dose of bromocriptine	Race Black/White (%)	Beta-blockers (%)	ACEI/ARBs (%)	Follow-up (months)
Azibani, 2020	Observational	2, Germany, South Africa	97/54	31[!]	2[!]	27[!]	NA	48/52	86[!]	88[!]	6
Biteker, 2020	Observational	1, Turkey	15/37	28[!]	2.6[!]	25.4	2.5 mg bd 2 weeks, then od for 6 weeks	NA	93[!]	77[!]	40.4
Haghika, 2013	Observational	3, Belgium, Germany, South Africa	64/32	33.8/34.1	2/2	27/26	2.5–5 mg od for 4 weeks	NA	NA	NA	6
Hilficker-Kleiner, 2017	Observational	3, Germany, South Africa, Scotland	21/9	31.6/26.7	3/3	32/31	2.5–5 mg od, then 2.5 mg for 4 weeks	57/44	100/100	81/99	6–68
Hoevelmann, 2019	Observational	1, South Africa	19/24	27.9[!]	2[!]	33	NA	53/40[$]	95.4	76.4	12
Kurbanov, 2020	Observational	1, Uzbekistan	21/22	30.0/29.5	1/2	34.0/36.7	2.5 mg bid, 2.5 mg od for 2 weeks	NA	95.2/100	85.7/86.4	12
Mahowald, 2019	Observational	1, USA	2/57	29.5[!]	NA	21[!]	NA	28.8/NA	89.8[!]	89.8[!]	76
Sliwa, 2010	RCT	1, South Africa	10/10	24/28	1.5/2	27.2/26.9	2.5 mg bid for 2 weeks, 2.5 mg od for 6 weeks	100/100[$]	100/100	100/100	6
Sliwa, 2020	Observational	49 Countries	84/463	31[!]	≥2 = 75%	31[!]	NA	28/33	81[!]	85[!]	6
Tremblay-Gravel, 2019	Observational	17, Canada	8/68	32/31	≥50%*	21/30	2.5 mg bid for 2 weeks, 2.5 mg od for 6 weeks	NA	88/82	88/85	25
van der Meer, 2024	Observational	49 Countries	85/467	31.5/30.9	>2 = 80%	34/31	NA	29.9/34.5	75.3/82.4	96.5/82.9	6
Yemeogo, 2017	RCT	1, Burkina Faso	48/48	29.1/29.5	3.6/3.2	37.2/37.5	2.5 mg bid for 4 weeks	100[#]	100/100	100/100	12

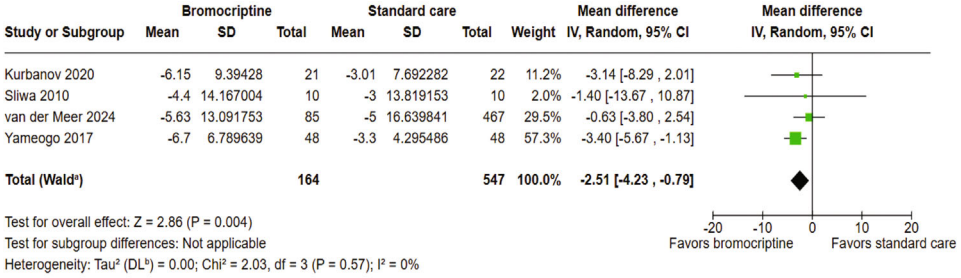
!, overall; #, all black; $, mixed race; *, multiparous; ACEI, angiotensin converting enzyme inhibitors; ARDs, Angiotensin receptor blockers; bd, twice daily; LVEF, left ventricular ejection fraction; NA, not available; od, daily; RCT, randomized controlled trial.

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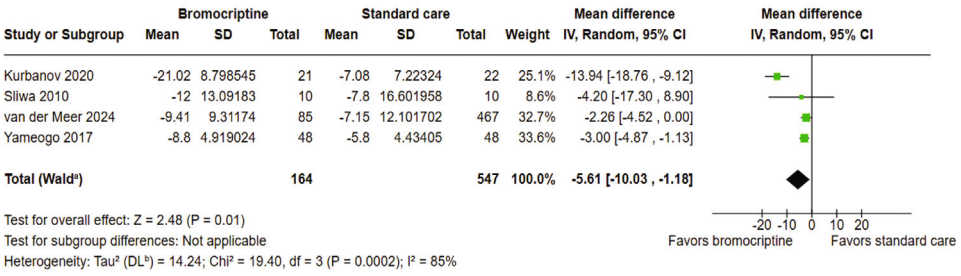
Figure 2 Forest plots showing the odds ratio (OR) outcomes comparing bromocriptine and standard care with standard care alone in PPCM. (A) Mean change in LV ejection fraction (B) Mean change in LV dimension in diastole (C) Mean change in LV dimension in systole (D) MACE (E) All-cause mortality (F) LV recovery (G) HF-related hospitalization (H) Thromboembolism (I) NYHA CI: confidence interval, M-H: Mantel-Haenszel, OR: Odd ratio.



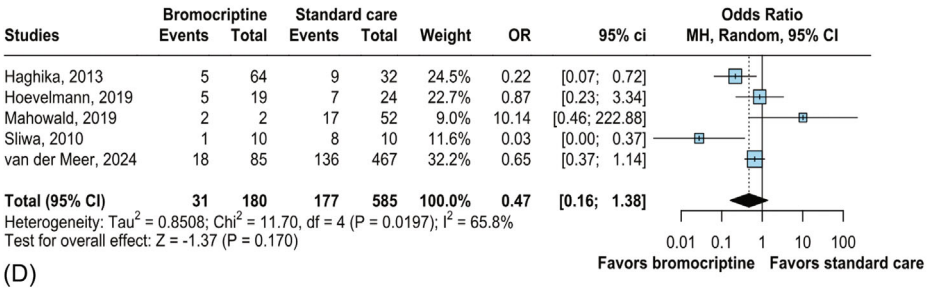
(A)



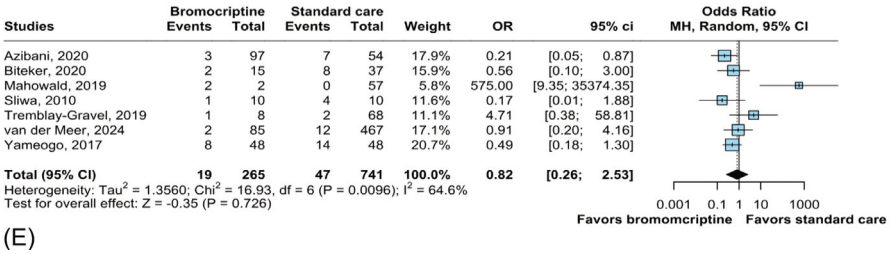
(B)



(C)



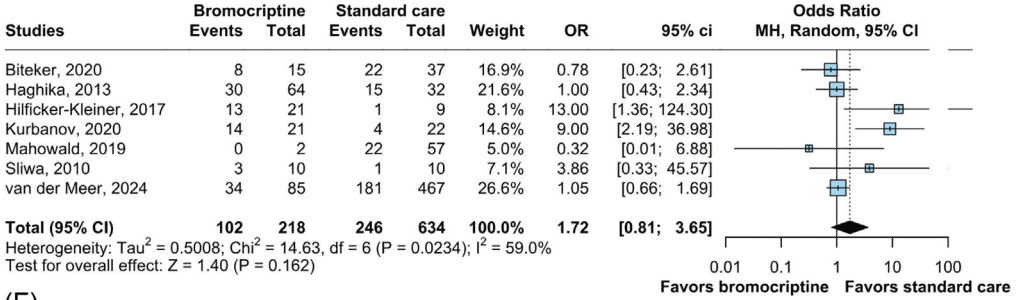
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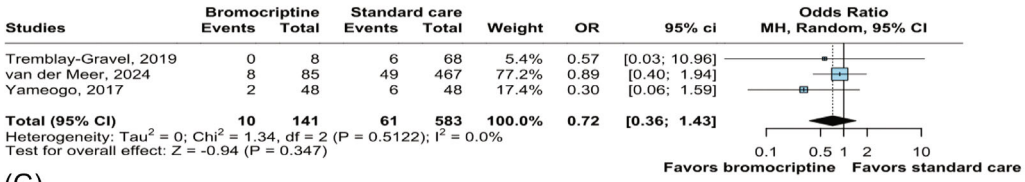
(E)

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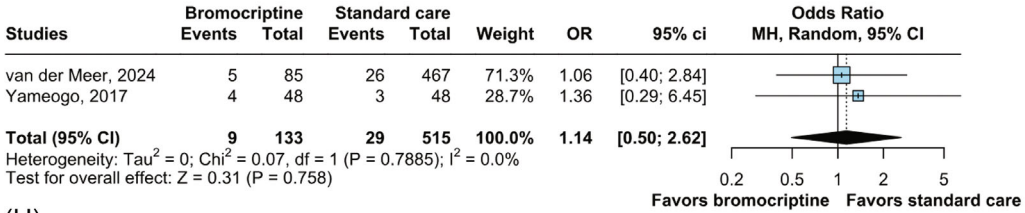
Figure 2 Continued



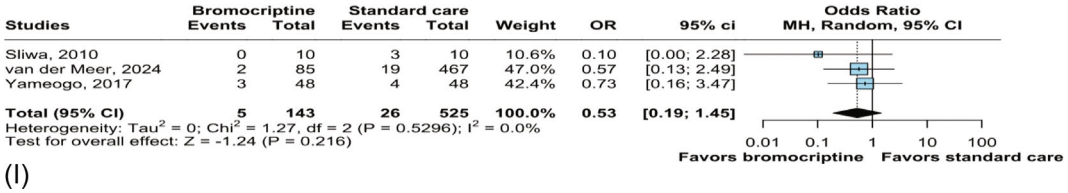
(F)



(G)



(H)



(I)

that the mean change in LV ejection was statistically driven by the RCTs (MD 13.66%; 95% CI: 0.79 to 26.53; $P = 0.040$; $I^2 = 76\%$) compared with non-RCT studies (MD 8.42%; 95% CI: −0.96 to 17.81; $P = 0.080$; $I^2 = 90\%$; *Figure* S1*A*).

Patients with baseline LV ejection fraction < 30% showed a greater improvement (MD 19.10%; 95% CI: 12.37 to 25.84; $P < 0.001$; $I^2 = 0\%$) compared with those with >30% (MD 5.95%; 95% CI: −0.73 to 12.6; $P = 0.08$; $I^2 = 87\%$; *Figure* S1*B*). Studies with follow-up > 6 months also showed a higher mean change (MD 10.79%; 95% CI: 4.49 to 17.10; $P < 0.001$; $I^2 = 76\%$; *Figure* S1*C*).

Mean change in LV dimensions

Four studies including 711 participants reported on changes in LV dimensions.[6,7,22,25] Bromocriptine plus standard care significantly reduced LV diastolic dimension compared with standard care alone (MD −2.51 cm; 95% CI: −4.23 to −0.79; $P = 0.004$; $I^2 = 0\%$; *Figure 2B*). This reduction was significant for RCTs (MD −3.33 cm; 95% CI: −5.57 to −1.10; $P = 0.003$; $I^2 = 0\%$) but not in non-RCT studies (MD −1.32 cm; 95% CI: −4.02 to 1.38; $P = 0.340$; $I^2 = 0\%$; *Figure* S2A).

Greater reductions were noted in patients whose baseline LVEF > 30% (MD −2.46 cm; 95% CI: −4.47 to −0.46; $P = 0.020$; $I^2 = 18\%$) and in follow-up > 6 months (MD −3.36 cm; 95% CI: −5.44 to −1.28; $P = 0.002$; $I^2 = 0\%$; *Figure* S2*B,C*).

For LV systolic dimension, bromocriptine plus standard care also led to a significant reduction (MD −5.61 cm; 95% CI: −10.03 to −1.18; $P = 0.010$; $I^2 = 85\%$; *Figure 2C*), driven by RCTs (MD −3.02 cm; 95% CI: −4.88 to −1.17; $P = 0.001$;

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I^2 = 0%), but not observed in non-RCTs (MD −7.90 cm; 95% CI: −19.34 to 3.54; *P* = 0.180; I^2 = 95%; *Figure* S3A). No significant difference was found based on baseline LVEF (MD −4.20 cm; 95% CI: −17.30 to 8.90; *P* = 0.530) or follow-up duration (MD −8.23 cm; 95% CI: −18.95 to 2.48; *P* = 0.130; I^2 = 0%; *Figure* S3*B,C*).

MACE

The composite of MACE was reported in five studies. Among the 765 participants,[6,8,19,21,25] the incidence of MACE was not statistically significant between the two groups (OR 0.47; 95% CI: 0.16 to 1.38; *P* = 0.170; I^2 = 65.8%; *Figure 2D*), with a high level of statistical heterogeneity. The incidence of MACE did not vary based on study design, baseline LV ejection fraction and follow-up duration (*Figure* S4*A–C*).

All-cause mortality

Data on the outcome of all-cause mortality were available from seven studies.[6,7,18,20,21,23,25] Among 1006 patients, there were 64 (6.4%) cases of all-cause mortality, 19 patients (7.2%) in the bromocriptine and standard care group and 47 patients (6.3%) in the standard care group. Bromocriptine in addition to standard care did not reduce the risk of all-cause mortality compared with standard care alone (OR 0.82; 95% CI: 0.26 to 2.53; *P* = 0.781; I^2 = 64.6%; *Figure 2E*). In a subgroup analysis based on study design, there was a tendency towards reduced incidence of all-cause mortality with the RCTs (OR 0.42; 95% CI: 0.17 to 1.04; *P* = 0.060; I^2 = 0%), but not with the non-RCTs (OR 1.86; 95% CI: 0.22 to 15.87; *P* = 0.568; I^2 = 73.9%). In addition, the incidence of all-cause mortality was not driven by the baseline LV ejection fraction (OR 1.26; 95% CI: 0.17 to 9.16; *P* = 0.820; I^2 = 76%) or longer duration of follow-up (OR 2.43; 95% CI: 0.31 to 18.94; *P* = 0.400; I^2 = 77%; *Figure* S5*A–C*). Notably, the meta-regression analysis showed no relationship between the number of childbirths in women with PPCM and all-cause mortality (coefficient = −0.04; CI: −0.98 to 0.90; *P* = 0.94; *Figure* S6).

LV recovery

Left ventricular recovery was reported in 7 studies involving 852 patients.[6,8,9,18,21,22,25] There was no difference in LV recovery in patients who were on bromocriptine with standard care compared with standard care alone (OR 1.72; 95% CI: 0.81 to 3.65; *P* = 0.162; I^2 = 54%; *Figure 2F*). There was a high level of statistical heterogeneity among the included studies for the outcome of LV recovery. In a subgroup analysis based on study design, there was no difference in LV recovery with the RCTs (OR 1.79; 95% CI: 0.76 to 4.21; *P* = 0.183; I^2 = 58.8%). Furthermore, the incidence of LV recovery was significant based on baseline LV ejection fraction of >30% (OR 9.98; 95% CI: 3.01 to 33.07; $P < 0.001$; I^2 = 0%) but not with the duration of follow-up (OR 2.60; 95% CI: 0.48 to 14.18; *P* = 0.270; I^2 = 71%; *Figure* S7*A–C*).

Meta-regression analysis showed a non-significant negative association between the number of pregnancies and the magnitude of recovery (coefficient = −0.57; CI: −1.80 to 0.67; *P* = 0.37; *Figure* S8).

Heart failure rehospitalization

Heart failure (HF) re-hospitalization was reported in three studies.[7,20,25] Among 724 patients, 71 experienced HF-related hospitalization: 10 patients (14.1%) in the bromocriptine plus standard care group and 61 patients (86%) in the control group.

The use of bromocriptine in addition to standard care did not reduce HF-related rehospitalization (OR 0.72; 95% CI: 0.36 to 1.43; *P* = 0.347; I^2 = 0%; *Figure 2G*). There was a low level of statistical heterogeneity in the pooled analysis for HF-related rehospitalization.

Thromboembolism

Thromboembolic events were reported in two studies.[7,25] Among 650 patients included in the pooled analysis, there were 38 reported events: 9 patients (23.7%) in the bromocriptine plus standard care group and 29 patients (76.3%) in the standard care group (OR 1.14; 95% CI: 0.50 to 2.62; *P* = 0.758; I^2 = 0%; *Figure 2H*). There was a low level of statistical heterogeneity in the pooled analysis for thromboembolism.

Persistence of NYHA class III/IV

The change in NYHA class with bromocriptine and standard care was reported in three studies.[6,7,25] In the pooled analysis, there was no difference between the groups in terms of the proportion of patients who remained in NYHA III/IV at the end of follow-up (OR 0.53; 95% CI: 0.19 to 1.45; *P* = 0.216; I^2 = 0%; *Figure 2I*). There was a low level of statistical heterogeneity in the pooled analysis for thromboembolism.

Quality assessment

The appraisal of RCTs is reported in *Figure* S9A while that of observational studies is in *Figure* S9B. Patients and investigators were unblinded at randomization in both RCTs. Overall, the RCTs were deemed to be at low risk of bias.[6,7] One of the observational studies performed propensity matching of the interventional and control patients.[22] All the non-RCT studies were considered to be at moderate risk of bias due to potential confounding and selection bias. No study was rated at critical risk. The funnel plot analysis of the outcomes showed a symmetric distribution of studies with similar weights and point estimates that converged towards the pooled treatment effect as weight increased, and therefore no evidence of publication bias (*Figure* S10*A–E*). The Egger's regression test indicated no significant publication bias, suggesting that funnel plot asymmetry is unlikely.

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Sensitivity analysis

A leave-one-out sensitivity analysis plot was performed for all outcomes with $I^2 > 50\%$ to evaluate the influence of individual studies on the overall effect estimates and heterogeneity. Overall, the statistical significance of the outcomes remained unchanged with the exclusion of each study across all outcomes, indicating the robustness of the pooled results. This analysis is illustrated for the outcome of the mean change in LV ejection fraction in Table S2. Notably, for the outcome of the mean change in LV dimension in diastole, the removal of Kurbanov et al. led to a substantial reduction in heterogeneity, from I^2 = 85% to I^2 = 29% and Yemeogo et al. to I^2 = 0% and lost statistical significance, while the removal of van de Meer also eliminated the heterogeneity, I^2 = 0%; however, the significance level was still maintained (Table S3).[7,22,24] No major shifts in heterogeneity were observed across other outcomes in the leave-one-out analyses.

Trial sequential analysis

Trial sequential analysis showed that only LV ejection fraction and LV end-diastolic dimension reached the RIS. Notably, the cumulative *Z*-curve for LV ejection fraction crossed the TSMB well before the RIS was achieved, whereas other outcomes, including mortality and MACE, did not reach the RIS. The overall sample size ranged from 159 to 852 participants, approximately 13–19% of the target RIS (*Figure 3A–D*).

Discussion

In this systematic review and meta-analysis of 12 studies with 1765 patients, the addition of bromocriptine to standard care was compared with standard care therapy alone in patients with PPCM. The main findings from the pooled analysis were: (1) bromocriptine was associated with a significantly higher change in mean LV ejection fraction compared with standard care alone; (2) bromocriptine led to significantly greater LV remodelling; (3) the incidence of MACE, all-cause mortality, thromboembolism or HF-related rehospitalizations was not significantly different between the groups, and (4) TSA suggests the need for further adequately powered studies.

The four foundational heart failure medications are well established for their disease-modifying properties, including reducing heart failure rehospitalization, mortality and reverse LV remodelling.[26] However, for patients with PPCM, the search for a disease-specific therapy remains ongoing. Bromocriptine, a dopamine agonist that inhibits prolactin secretion, has emerged as a promising candidate.[6,7,26,27] By suppressing prolactin, bromocriptine reduces the formation of the 16-kDa fragment and mitigates its deleterious effects on the myocardium and vascular endothelium.[28,29] Our study showed that the mean change in LV ejection fraction was significantly higher with the addition of bromocriptine to standard care therapy in PPCM. Additionally, bromocriptine was associated with greater LV remodelling.

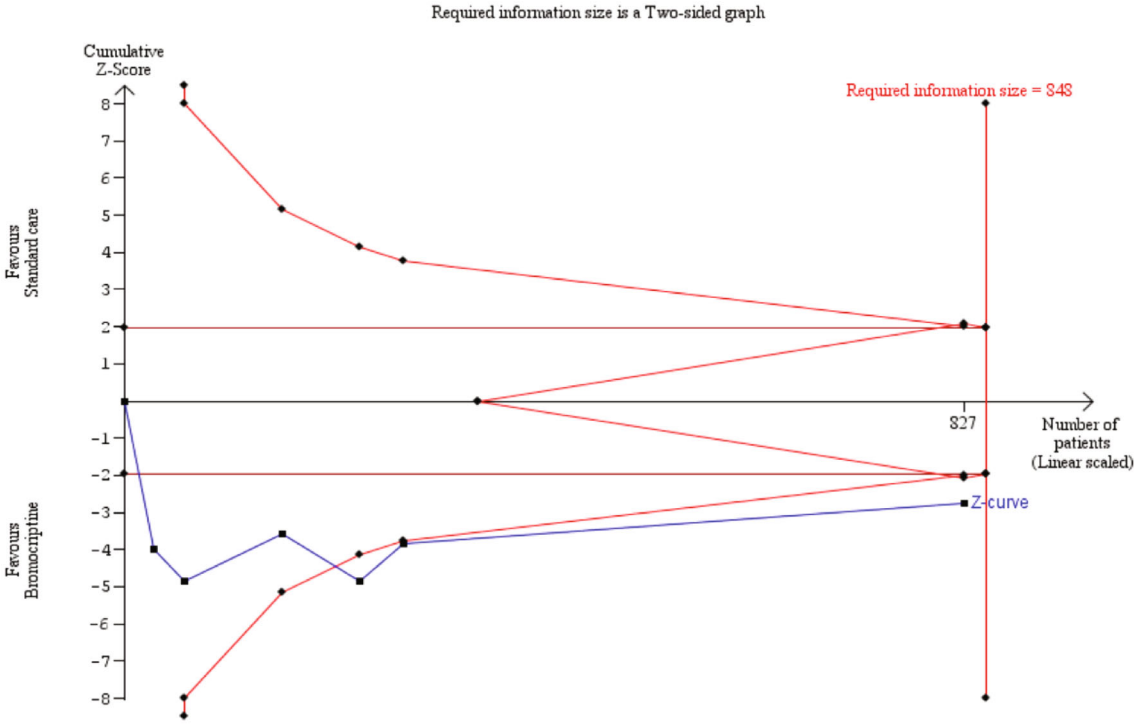
The recently published EURObservational Research Programme (EORP) PPCM registry and other observational studies comparing treatment with bromocriptine and standard care with standard care alone in PPCM found a reduction in the composite endpoint of MACE that is made up of maternal death, rehospitalization and persistent LV dysfunction.[8,21,25] Similarly, RCTs and a meta-analysis have demonstrated that adjunctive bromocriptine therapy is associated with significantly improved survival at 6-month follow-up.[6,7,12] However, the findings of this meta-analysis contrast with those of earlier individual studies with respect to the incidence of MACE, indicating ongoing uncertainty regarding the broader clinical benefit of bromocriptine beyond survival outcomes. MACE did not differ with bromocriptine also in a recent meta-analysis.[11] The inconsistency in MACE outcomes despite improved survival and LV function and remodelling likely reflects limitations in study design, variability in event definitions, follow-up duration, reliance on surrogate endpoints and low event rates.

In the meta-regression analysis, higher parity did not show a significant association with LV function recovery or all-cause mortality. Specifically, while the coefficient for LV recovery was negative, suggesting a potential trend towards worse outcomes with increasing parity, the association was not statistically significant (coefficient = −0.57; 95% CI: −1.80 to 0.67; P = 0.37). Similarly, no meaningful relationship was observed between parity and all-cause mortality (coefficient = −0.04; 95% CI: −0.98 to 0.90; P = 0.94). These findings suggest that parity is unlikely to be a major determinant of left ventricular recovery or survival outcomes in this population.

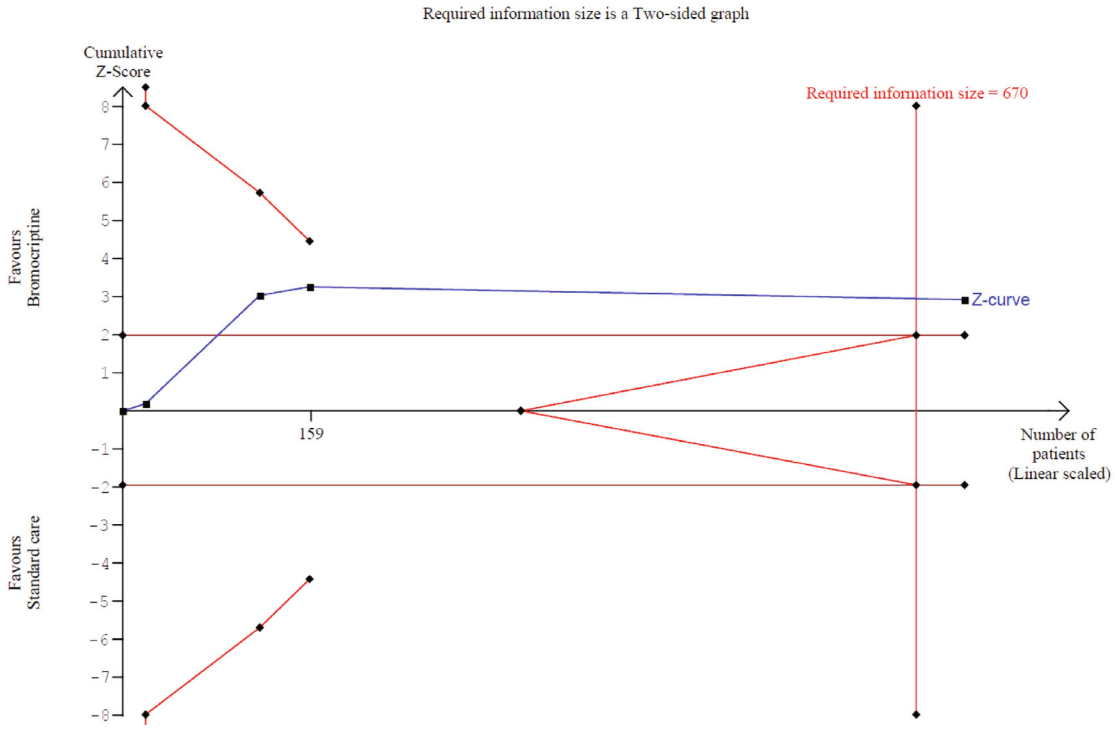
There are concerns of bromocriptine increasing the risk of thromboembolism, particularly in the setting of PPCM, where patients are already in a hypercoagulable state due to pregnancy and the puerperium.[7,30] Although a few case reports have described acute vascular compromise in PPCM patients treated with bromocriptine,[31] a pooled analysis of three studies did not show a significantly higher incidence of thromboembolic events in patients receiving bromocriptine compared with standard care alone.[12] The result of the present meta-analysis is in keeping with this finding, albeit a wide confidence interval. Importantly, the use of anticoagulation varied across the included studies, with some studies adopting routine prophylactic anticoagulation in all patients receiving bromocriptine,[8,9] others applied anticoagulation selectively based on risk factors.[6,22–24] This variability represents a potential confounder when interpreting thromboembolism outcomes. Additionally, factors such as dilatation of the LV, oxidative stress induced endothelial injury, and reduced mobility may contribute to the elevated thrombotic risk in this population independent of bromocriptine use. Future studies should standardize anticoagulation protocols to more accurately assess the independent effect of bromocriptine on thromboembolic risk.

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Figure 3 Trial sequential analysis (A) Mean change in LV ejection fraction, (B) Mean change in LV dimension in diastole, (C) LV recovery, (D) MACE.



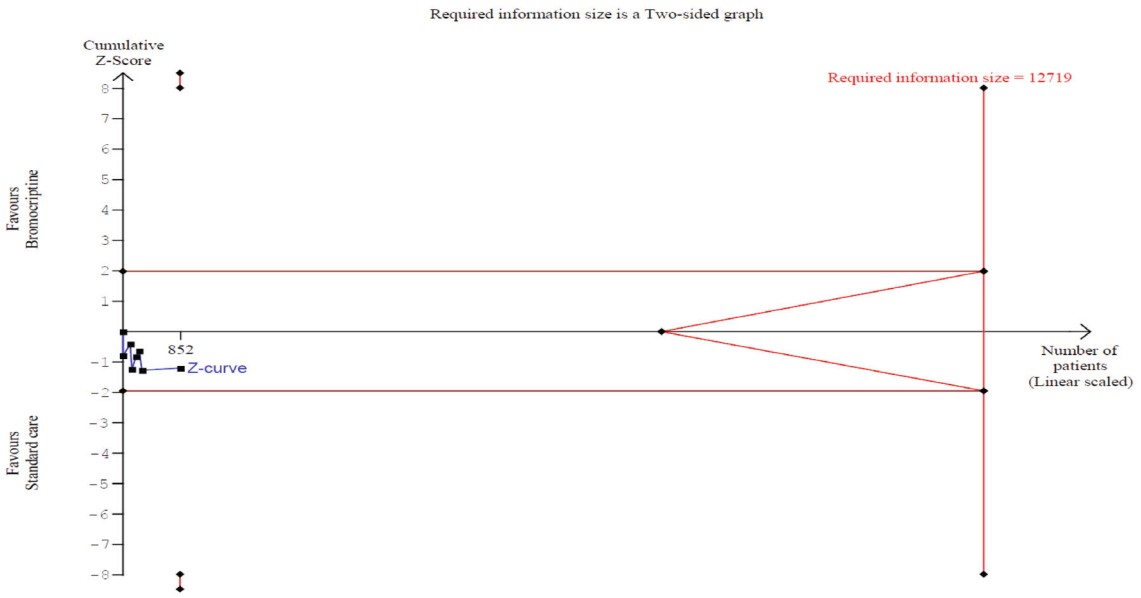
(A) Mean change in LV ejection fraction



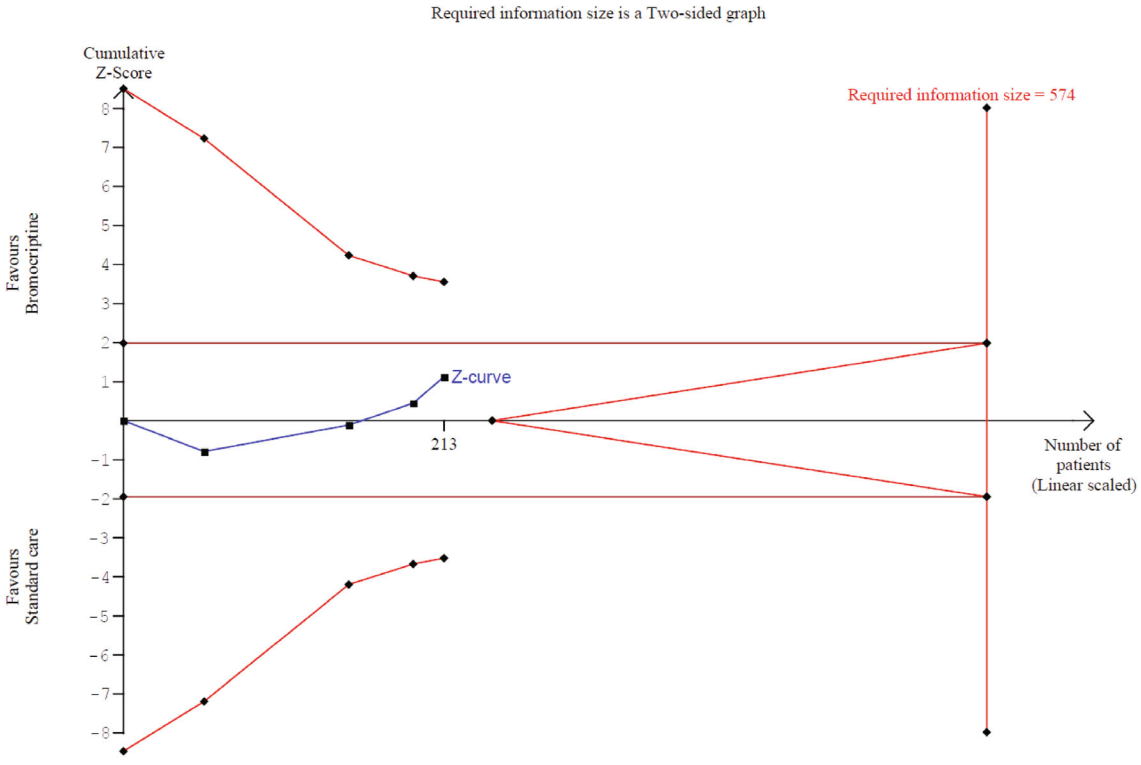
(B) mean change in LV dimension in diastole

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Figure 3 Continued



(C) LV recovery



(D) MACE

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Our findings suggest that the addition of bromocriptine to standard care may be associated with significant improvements in key echocardiographic parameters, particularly LV ejection fraction and dimensions. Trial sequential analysis indicated that, although LV ejection fraction and diastolic dimension showed a potential signal of benefit by crossing the monitoring boundary, the overall evidence remains underpowered, as most outcomes did not reach the RIS. This suggests that current data are insufficient to draw definitive conclusions regarding the long-term effects of bromocriptine for MACE, all-cause mortality, HF-related rehospitalizations or thromboembolism in PPCM.

It is important to note the differences between RCTs and observational studies included in this meta-analysis. While observational studies consistently demonstrated significant improvements in LV function and remodelling with bromocriptine and standard care, the RCTs yielded more modest or less consistent effects. This discrepancy may reflect differences in study design, patient selection, background therapy and sample size, all of which can influence the estimates of treatment effect. Given that RCTs generally provide higher-quality evidence, the divergence highlights the need for cautious interpretation of the pooled results. We therefore emphasize that, although our findings are encouraging, they remain hypothesis-generating and require confirmation in adequately powered RCTs before firm clinical recommendations can be made. The ongoing *Randomized Evaluation of Bromocriptine in Myocardial Recovery Therapy for Peripartum Cardiomyopathy (REBIRTH)* trial may help to clarify the net clinical benefit of bromocriptine, provide evidence-based recommendations for its use, and determine whether universal or selective anticoagulation should be adopted alongside therapy.

Limitations

This study has several limitations. First, there was moderate to high heterogeneity observed across several outcomes, particularly mean change in LV ejection fraction. This may reflect differences in study design, patient populations and outcome definitions, as well as the inclusion of observational studies with the inherent risk of bias. In addition, the timing of follow-up echocardiographic assessments was not uniform across studies, and in many cases exact intervals were not reported, which limited our ability to standardize follow-up periods and may have contributed to the variability in pooled estimates. Nevertheless, sensitivity analyses, including leave-one-out testing, suggested that no single study disproportionately influenced the overall findings. Second, several outcomes, including mortality and rehospitalization, were associated with wide confidence intervals, reflecting imprecision and limiting the certainty of these estimates. Third, despite efforts to exclude duplicate publications, some included studies may have reported overlapping patient populations, potentially introducing data duplication. To address this, we included the most recent report when overlap was suspected and performed a sensitivity analysis excluding studies with potential duplication. Finally, our analysis suggested that parity did not significantly influence LV recovery or survival; however, this finding should be interpreted cautiously due to the lack of individual patient-level data and variable follow-up protocols. Similarly, the lack of access to individual patient data limited our ability to perform detailed subgroup analyses, such as distinguishing between first-time and recurrent cases of peripartum cardiomyopathy. Nonetheless, we conducted a meta-regression to explore the effect of first-diagnosed PPCM on all-cause mortality and found no statistically significant association. It should be acknowledged that the performance of multiple subgroup and sensitivity analyses may increase the risk of type I error. Therefore, some statistically significant findings from these exploratory analyses should be interpreted with caution and considered hypothesis-generating rather than definitive.

Conclusions

In this meta-analysis of 12 studies, adjunctive bromocriptine plus guideline-directed medical therapy was associated with improvements in left ventricular function and favourable cardiac remodelling in patients with PPCM. However, effects on mortality, MACE and rehospitalization remain uncertain, and while TSA indicates that some outcomes may be robust, the overall evidence is still inconclusive. This work represents the most comprehensive long-term evaluation of bromocriptine to date, extending beyond prior reviews that focused mainly on short-term or regional differences in care. These findings may provide exploratory evidence for a potential disease-modifying role of bromocriptine and underscore the need for large, adequately powered randomized trials to clarify its long-term clinical impact.

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Conflict of Interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Seach stratgy in the databases.
Table S2. Definition of major adverse cardiovascular events and left ventricular recovery by the included studies.
Figure S1. Subgroup analysis based on mean change in LV ejection fraction based on (Figure S1A) study design, (Figure S1B), baseline LV ejection fraction, (Figure S1C) follow-up duration.
Figure S2. Subgroup analysis of mean change in LV dimension in diatole based on (Figure S2A) study design, (Figure S2B) baseline ejection fraction, (Figure S2C) follow-up duration.
Figure S3. Subgroup analysis of mean change in LV dimension in systole based on study design (Figure S3A), baseline LV ejection fraction (Figure S3B), and follow-up duration (Figure S3C).
Figure S4. Subgroup analysis of MACE based on (Figure S4A) study design, (Figure S4B) baseline LV ejection fraction, and (Figure S4C) follow-up duration.
Figure S5. Subgroup analysis of all-cause mortality based on study design, baseline LV ejection fraction and follow-up duration.
Figure S6. Meta-regression of the effect of parity on all-cause mortality.
Figure S7. Subgroup analysis of LV recovery based on study design, baseline LV ejection fraction and follow-up duration.
Figure S8. Meta-regression of the effect of parity on LV recovery.
Figure S9. Risk of Bias assessment (A) RoB2 (B) ROBINS-I. RoB2: Risk of bias assessment version 2, ROBINS-I = Risk of Bias in Non-randomized Studies of Interventions-I.
Figure S9. Funnel plot of publication bias and Egger's test on outcomes.
Table S2. Leave-one-out sensitivity analysis for LV ejection fraction.
Table S3. Leave-one-out sensitivity analysis of LV dimension in diastole.

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