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✉ Ke

kewanhai@qq.com

Fuwai Shenzhen Hospital, Chinese Academy of Medical Sciences

✉ Huang

Fuwai Shenzhen Hospital, Chinese Academy of Medical Sciences

Systematic Review

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Efficacy and Safety of Recombinant Human Brain Natriuretic Peptide (rhBNP/Nesiritide) in Heart Failure with Preserved Ejection Fraction: A Systematic Review and Meta-Analysis

Wanhai Ke^{1*}, PhD; Weichao Huang¹, MM

1. Fuwai Shenzhen Hospital, Chinese Academy of Medical Sciences (Shenzhen Key Laboratory of Cardiovascular Disease; Shenzhen Clinical Research Center for Cardiovascular Disease), No. 12, Langshan Road, Xili Street, Nanshan District, Shenzhen 518000, China

*Corresponding author: Wanhai Ke, PhD. E-mail: kewanhai@qq.com

Abstract

Background

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of all heart failure cases, and its prevalence continues to rise with population aging. However, evidence on recombinant human brain natriuretic peptide (rhBNP; nesiritide) for HFpEF has not been systematically synthesized. We therefore performed a systematic review and meta-analysis to evaluate the efficacy and safety of rhBNP in patients with HFpEF.

Methods

PubMed, Europe PMC, ClinicalTrials.gov, CNKI, Wanfang and VIP databases were searched on August 10, 2026 without language restrictions. Controlled clinical studies of intravenous nesiritide/rhBNP in adult patients with HFpEF or diastolic heart failure were included. Odds ratios (OR) and mean differences (MD) or standardized mean differences (SMD) were pooled using DerSimonian-Laird random-effects models, followed by leave-one-out sensitivity analyses. Risk of bias was assessed with the Cochrane RoB 2 tool or the Newcastle-Ottawa Scale.

Results

Of 82 deduplicated records, 7 studies with 1,314 patients were included (2 English, 5 Chinese). Compared with control, rhBNP significantly improved the overall clinical response rate (OR 2.97, 95% CI 1.40–6.28, $P=0\%$), left ventricular ejection fraction (MD 5.82%, 95% CI 4.07–7.57, $P=0\%$), E/A ratio (MD 0.27, 95% CI 0.21–0.33, $P=0\%$) and 6-minute walk distance (MD 26.56 m, 95% CI 12.98–40.13, $P=4.6\%$), and reduced NT-proBNP (SMD -2.49 , 95% CI -4.29 to -0.69). No significant differences were found for death or heart failure rehospitalization (OR 0.79, 95% CI 0.22–2.82) or worsening renal function (OR 1.32, 95% CI 0.38–4.60), and sensitivity analyses indicated unstable results for these hard endpoints. No serious adverse events were reported; hypotension was more frequent with nesiritide in one study.

Conclusions

rhBNP may improve clinical efficacy, cardiac function and exercise capacity in HFpEF, whereas benefits on hard endpoints remain unproven. Given the predominance of small, short-term studies, large prospective randomized trials are warranted.

Keywords: nesiritide; recombinant human brain natriuretic peptide; heart failure with preserved ejection fraction; diastolic heart failure; meta-analysis; systematic review

Background

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of all patients with heart failure, and its prevalence continues to rise with population aging; rates of rehospitalization and mortality are comparable to those of heart failure with reduced ejection fraction (HFrEF) [1]. HFpEF is characterized by left ventricular diastolic dysfunction and elevated filling pressures and is frequently accompanied by hypertension, obesity, diabetes mellitus and atrial fibrillation. Its pathophysiology involves microvascular inflammation, myocardial fibrosis and neuroendocrine activation. To date, no targeted therapy has unequivocally improved prognosis, and clinical management relies mainly on diuretics, comorbidity control and exercise rehabilitation.

Nesiritide (recombinant human brain natriuretic peptide, rhBNP), a recombinant preparation of endogenous B-type natriuretic peptide (BNP), activates natriuretic peptide receptors and increases cyclic guanosine monophosphate levels, thereby producing vasodilation, natriuresis and diuresis and inhibiting the renin-angiotensin-aldosterone system (RAAS); it is widely used in clinical practice for acute decompensated heart failure [2,3]. However, the ASCEND-HF trial showed that nesiritide did not improve death or rehospitalization in acute heart failure, although that trial enrolled predominantly patients with HFrEF [2]. The response to natriuretic peptide agents may differ between HFpEF and HFrEF. Although numerous controlled studies, particularly from China, have evaluated rhBNP for diastolic heart failure (DHF), a systematic synthesis of this evidence is lacking.

Current treatment for HFpEF centers on symptom management and comorbidity control. Although sodium-glucose cotransporter-2 inhibitors and other agents have been recommended, treatment options targeting the natriuretic peptide system to directly improve diastolic function and volume status remain limited. Given its combined vasodilatory, natriuretic and neuroendocrine-modulating effects, rhBNP is theoretically aligned with the pathophysiological features of volume overload and elevated filling pressures in HFpEF; its benefit-risk ratio, however, requires evidence-based definition. We therefore systematically searched major international databases (Chinese and English) and performed a meta-analysis to evaluate the efficacy and safety of rhBNP in HFpEF.

Methods

Search strategy

PubMed, Europe PMC, ClinicalTrials.gov, CNKI, Wanfang and VIP databases were searched on August 10, 2026, without language or publication type restrictions. The English search strategy was: (nesiritide[tiab] OR rhBNP[tiab] OR "recombinant human brain natriuretic peptide"[tiab]) AND (HFpEF[tiab] OR "preserved ejection fraction"[tiab] OR "diastolic heart failure"[tiab]) AND 2000:2026[dp], yielding 16 records; a CQL re-run in Europe PMC retrieved 13 records, all of which were contained within the PubMed results. The Chinese search strategy, provided in full as supplementary material, combined the Chinese-language equivalents of the nesiritide/rhBNP terms (Xinhuosu, recombinant human brain natriuretic peptide, nesiritide) and the HFpEF terms (preserved ejection fraction, diastolic heart failure); it was executed separately in CNKI, Wanfang and VIP and yielded 66 records after deduplication. Registered trials were

additionally searched in ClinicalTrials.gov (5 trials, none being an interventional trial of rhBNP for HFpEF), and OpenAlex was used for citation verification. Search strategies for each database were archived in a standardized format (multi-line version, single-line version, web link, and notes). This review was reported in accordance with the PRISMA 2020 statement [4].

Inclusion and exclusion criteria

Inclusion criteria were: (1) adult patients with HFpEF/DHF (LVEF $\geq 50\%$ or $>40\%$, or a definite diagnosis of diastolic heart failure); (2) intervention including intravenous nesiritide/rhBNP; (3) a control group (placebo or standard heart failure therapy); and (4) extractable efficacy, cardiac function or safety outcomes. Exclusion criteria were: pure HFrEF; uncontrolled single-arm studies and case reports; reviews and consensus statements; secondary analyses of trials (e.g., ASCEND-HF) that did not report effect estimates within the HFpEF subgroup; studies in which both groups received rhBNP so that the intervention effect could not be isolated; and duplicate publications of the same data. Two reviewers independently screened titles/abstracts and full texts and extracted data; disagreements were resolved by discussion or by a third reviewer.

Data extraction and quality assessment

Using a predefined extraction form, we collected study design, sample size, baseline characteristics, intervention protocol, follow-up duration and outcome effect estimates, including age, sex, NYHA class, comorbidities, drug dose and bolus/maintenance regimen, treatment course, concomitant medication, and event numbers and means $\pm$ SD for each outcome. The overall clinical response rate was defined as the sum of "markedly effective" and "effective" responses. Risk of bias was assessed with the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials and the Newcastle-Ottawa Scale (NOS) for non-randomized controlled and cohort studies. Certainty of evidence was assessed following the GRADE framework.

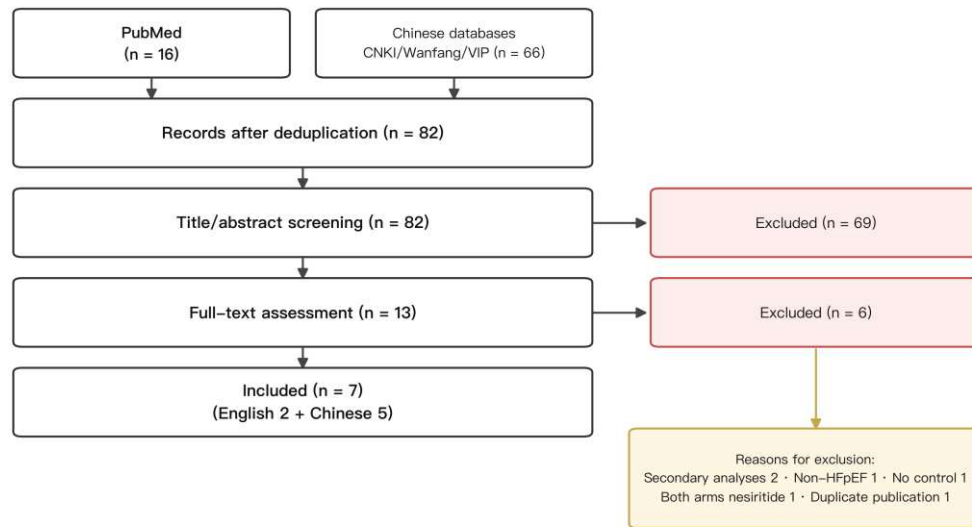
Statistical analysis

For dichotomous outcomes, the odds ratio (OR) was used as the effect measure, with the Haldane-Anscombe zero-event correction, and estimates were pooled on the log scale with inverse-variance weighting. For continuous outcomes, the mean difference (MD) was pooled, or the Hedges g standardized mean difference (SMD) when units or assays differed. Pooling was performed with the DerSimonian-Laird random-effects model. Heterogeneity was assessed using the I^2 statistic and the Q test. Leave-one-out sensitivity analyses were performed, and fixed-effect models were additionally applied to key outcomes to evaluate the influence of model choice. Because fewer than 10 studies were included, funnel plots and Egger tests were not performed. Analyses were conducted in Python 3, and a two-sided $P < 0.05$ was considered statistically significant.

Results

Literature screening

A total of 82 deduplicated records were obtained (16 from English databases and 66 from Chinese databases; the 13 Europe PMC records were all contained within the PubMed results). After screening of titles and abstracts, 69 records were excluded (prognostic and biomarker studies without intervention, reviews, consensus statements, non-HFpEF populations, etc.), and 13 full texts were assessed for eligibility. Six full texts were excluded: two secondary analyses of ASCEND-HF without HFpEF-specific effect estimates, one non-HFpEF population, one uncontrolled single-arm study, one study in which both groups received rhBNP, and one duplicate publication of the same data. Ultimately, 7 studies were included (2 English and 5 Chinese), as shown in Figure 1.



Search date 2026-08-10 · Reported per PRISMA 2020

Figure 1. PRISMA 2020 flow diagram of study selection.

Characteristics of included studies

Among the English studies, Wan 2016 [5] reported a prespecified HFpEF subgroup of the ROSE-AHF randomized double-blind trial (EF >40%; nesiritide 47 vs placebo 43 patients; $0.005 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ without a bolus for 72 h), with cumulative urine output at 72 h (8,400 vs 8,750 mL, $P=0.22$), treatment failure (OR 5.6, 95% CI 1.7–18.3), cardiorenal syndrome and death, suggesting limited decongestive efficacy in the HFpEF subgroup; Kelesidis 2012 [6] was a retrospective cohort of 658 patients with decompensated HFpEF (nesiritide 328 vs standard diuretics 330; mean infusion 3.33 ± 1.85 days), reporting changes in GFR at 1 month ($+1.00$ vs -3.17 mL/min, $P<0.001$), hypotension (17.1% vs 9.5%) and 30-day death/rehospitalization.

Among the Chinese studies, Li Xinru 2023 [7] used convenience sampling to enroll 87 patients with HFpEF (LVEF $\geq 50\%$): 44 in the rhBNP plus amiodarone group versus 43 in the amiodarone group, with balanced age (62.82 ± 3.50 vs 62.71 ± 3.56 years) and NYHA class distribution; Tao Shuoqi 2018 [3] randomized 90 patients with DHF (hypertension >5 years, LVEF $\geq 50\%$), with 45 patients receiving lyophilized rhBNP (bolus $1.5\text{--}2.0$ $\mu\text{g/kg}$ followed by 0.008 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for 3 days) added to conventional therapy, treated for 1 week and followed for 1 month; Wang Lixia 2012 [8] was a randomized open-label controlled trial of 98 patients with DHF (rhBNP group 50 vs control 48), observed at 2 weeks and 6 months; Zhang Aiwen 2015 [9] randomized 190 patients with DHF (age <75 years, LVEF $>50\%$, E/A <1 , BNP >200 pg/mL) by visit date into 98 and 92 patients, receiving rhBNP (bolus 1.5 $\mu\text{g/kg}$ followed by 0.0075 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for 72 h) for 7 days; Li Meng 2009 [1] randomized 65 patients with de novo DHF into rhBNP ($n=35$) and control ($n=30$) groups, with rhBNP given as a 1.5 $\mu\text{g/kg}$ bolus followed by 0.0075 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ infusion for 5 h once weekly for 12 weeks. Study populations, interventions and follow-up are summarized in Table 1.

Meta-analysis results

Overall clinical response rate (2 studies): Li Xinru 2023 [7] 40/44 (90.9%) vs 31/43 (72.1%), and Zhang Aiwen 2015 [9] 91/98 (92.9%) vs 77/92 (83.7%); the pooled OR was 2.97 (95% CI 1.40–6.28, $I^2=0\%$), significantly favoring rhBNP (Figure 2). Cardiac function: pooled MD for LVEF was 5.82% (95% CI 4.07–7.57, $I^2=0\%$) (Figure 3); pooled MD for E/A ratio was 0.27 (95% CI 0.21–0.33, $I^2=0\%$) (Figure 4); pooled SMD for NT-proBNP was -2.49 (95% CI -4.29 to -0.69) (Figure 5). Exercise capacity and vascular function: pooled MD for 6-minute walk distance was 26.56 m (95% CI 12.98–40.13, $I^2=4.6\%$) (Figure 6); pooled MD for serum nitric oxide was 11.81 (95% CI 0.53–23.09, $I^2=91.5\%$) (Figure 7); pooled MD for isovolumic relaxation time was -10.94 ms (95% CI -18.88 to -3.00 , $I^2=93.4\%$) (Figure 8).

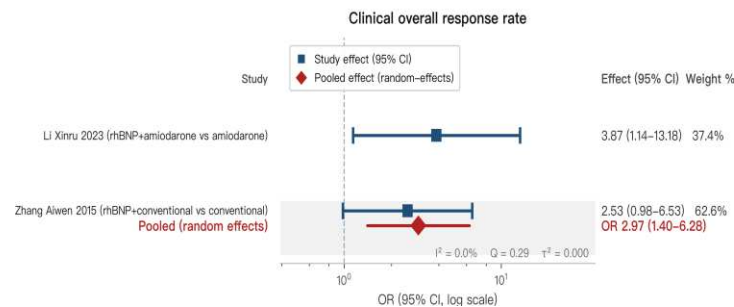


Figure 2. Forest plot of overall clinical response rate (OR, random-effects model).

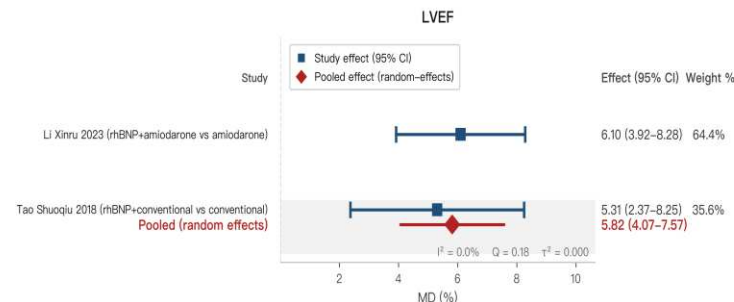


Figure 3. Forest plot of left ventricular ejection fraction (MD, random-effects model).

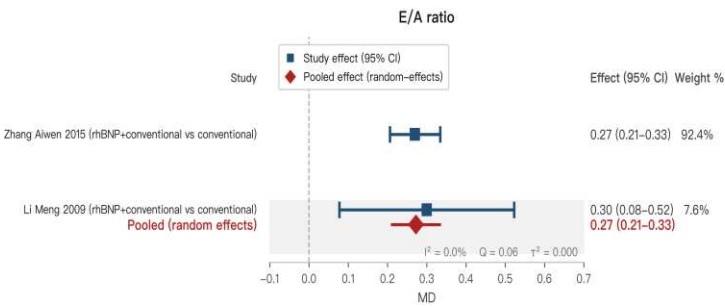


Figure 4. Forest plot of E/A ratio (MD, random-effects model).

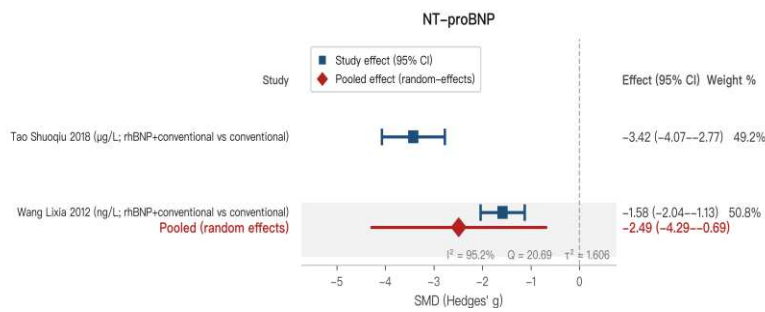


Figure 5. Forest plot of NT-proBNP (SMD, random-effects model).

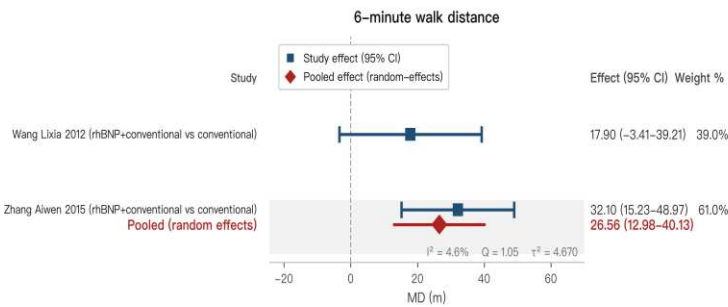


Figure 6. Forest plot of 6-minute walk distance (MD, random-effects model).

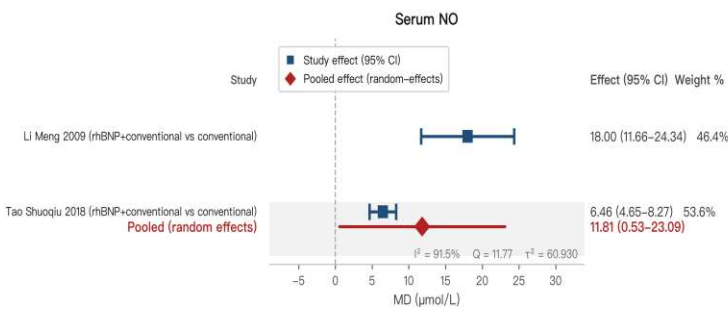


Figure 7. Forest plot of serum nitric oxide (MD, random-effects model).

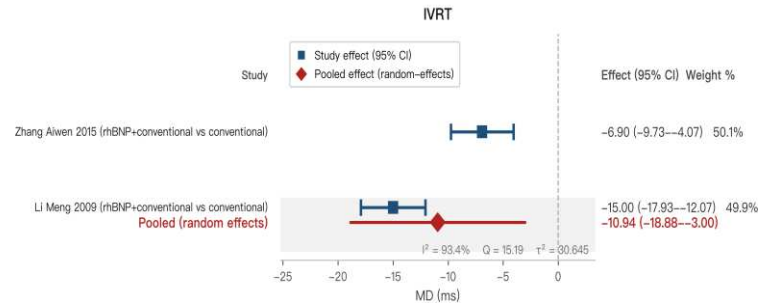


Figure 8. Forest plot of isovolumic relaxation time (MD, random-effects model).

Hard endpoints: the pooled OR for death or heart failure rehospitalization (2 studies) was 0.79 (95% CI 0.22–2.82, $I^2=65.9\%$) (Figure 9), and that for worsening renal function (2 studies) was 1.32 (95% CI 0.38–4.60, $I^2=74.8\%$) (Figure 10); neither reached statistical significance. Safety: no serious adverse events were reported in any study; hypotension was more common in the nesiritide group in Kelesidis 2012 [6] (17.1% vs 9.5%), whereas the incidence of adverse events did not differ significantly between groups in Zhang Aiwen 2015 [9].

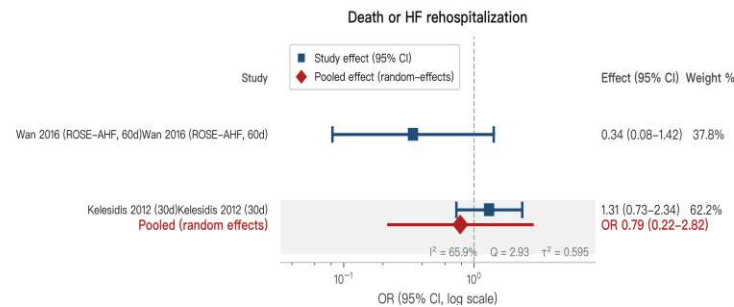


Figure 9. Forest plot of death or heart failure rehospitalization (OR, random-effects model).

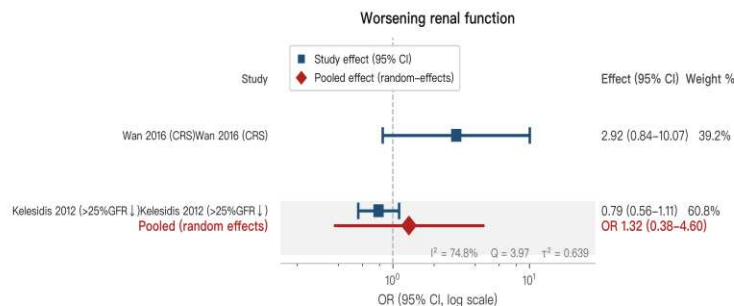


Figure 10. Forest plot of worsening renal function (OR, random-effects model).

Sensitivity analysis

The significance and direction of the pooled estimates for the overall clinical response rate, LVEF, E/A ratio and 6-minute walk distance remained stable in leave-one-out analyses; for NO, IVRT and NT-proBNP, I^2 dropped to 0% after removing either study and the direction was unchanged. In contrast, the pooled estimates for death or heart failure rehospitalization and worsening renal function reversed direction when either study was removed (0.34 to 1.31 and

0.79 to 2.92, respectively), indicating unstable results. Overall, pooled estimates for surrogate outcomes were relatively robust, whereas the hard-endpoint evidence was limited by the small number of studies.

Discussion

Based on a systematic search of major Chinese and English databases, this meta-analysis quantitatively synthesized the efficacy and safety of rhBNP in HFpEF, including 7 studies with 1,314 patients. rhBNP significantly improved the overall clinical response rate, LVEF, E/A ratio and 6-minute walk distance and reduced NT-proBNP, but had no significant effect on death or heart failure rehospitalization or worsening renal function, yielding a pattern of "surrogate-outcome benefit with neutral hard endpoints". Under the GRADE framework, most included studies were small, short-term and partly non-randomized, with a risk of duplicate publication; overall evidence quality was low to very low. The conclusions should therefore be regarded primarily as hypothesis-generating and supportive of clinical decision-making rather than as a basis for strong recommendations.

These benefits have a plausible pharmacological basis. rhBNP is structurally identical to endogenous BNP and, through natriuretic peptide receptor A, increases cGMP in vascular smooth muscle and endothelial cells, producing vasodilation, natriuresis, diuresis and RAAS inhibition, and can antagonize endothelin-mediated myocardial fibrosis and ventricular remodeling [2,3]. In addition, rhBNP directly inhibits proximal tubular sodium reabsorption and increases glomerular filtration rate, which is theoretically relevant to the volume overload and renal function fluctuations commonly seen in HFpEF. The observed increases in NO, decreases in ET-1, improvements in FMD and marked reductions in NT-proBNP are consistent with the mechanisms of improved vascular endothelial function and reduced filling pressures; improvements in diastolic indices such as E/A ratio and IVRT suggest favorable effects on left ventricular diastolic properties; and the reductions in inflammatory cytokines (IL-6, TNF- α) reported by Li Xinru 2023 [7] further support an effect on the myocardial inflammatory milieu.

Compared with previous evidence, ASCEND-HF [2] showed no benefit of nesiritide on hard endpoints in acute heart failure, but enrolled predominantly HFrEF; the HFpEF subgroup of ROSE-AHF [5] also suggested weaker decongestive effects than in HFrEF (interaction $P < 0.05$). The favorable findings of the included RCTs from China are not contradictory: these studies mostly used an add-on design (rhBNP plus conventional therapy versus conventional therapy), had short follow-up (3 days to 12 weeks) and used surrogate outcomes as the primary endpoints, reflecting short-term functional benefits; in Wang Lixia 2012 [8], the between-group difference disappeared at 6 months, suggesting that the benefit may attenuate over time.

This study has several limitations. First, the included studies from China had small sample sizes and short follow-up, and 2 of the 4 RCTs used suboptimal randomization methods (allocation by visit date or convenience sampling), with moderate-to-high risk of bias. Second, the add-on design cannot fully isolate the independent effect of rhBNP, and response criteria differed across studies. Third, pooled estimates for NO, IVRT and NT-proBNP showed high heterogeneity (I^2 91%–95%) due to differences in dosing, treatment duration and assay methods, and should be interpreted only as directional. Fourth, hard endpoints were available from only 2 English studies with unstable results. Fifth, the Chinese-language literature carries a risk of

duplicate publication and low-quality journals (one duplicate was identified and excluded in this review), which may overestimate benefit. Finally, because fewer than 10 studies were included, publication bias could not be formally tested.

In conclusion, rhBNP may improve surrogate outcomes including clinical response, cardiac function, diastolic function and exercise capacity in HFpEF, whereas hard-endpoint benefits remain unproven. Future trials should use hard endpoints or core surrogate outcomes, follow patients for at least 6 months, standardize dosing and treatment duration, and perform subgroup analyses by HFpEF phenotype (e.g., obesity-related, hypertension-related, atrial fibrillation-related) to identify populations most likely to benefit.

From a clinical practice perspective, short-term addition of rhBNP to conventional heart failure therapy may improve symptoms and functional measures in HFpEF and may serve as an adjunctive treatment during acute exacerbation or volume overload. However, given the lack of hard-endpoint evidence and the risk of hypotension, rhBNP is not recommended as first-line long-term therapy for HFpEF. In clinical use, dosing and duration should be individualized according to symptoms, volume status and dynamic renal function monitoring, with close observation of blood pressure.

Conclusions

rhBNP improved the clinical response rate, cardiac function and exercise capacity in patients with HFpEF, whereas hard-endpoint benefits were not established. The current evidence derives mainly from small, short-term studies and requires confirmation in large prospective randomized controlled trials.

Declarations

Ethics approval and consent to participate: Not applicable (systematic review of published studies).

Consent for publication: Not applicable.

Availability of data and materials: The datasets analyzed in the present study are available from the corresponding author on reasonable request. Search strategies and extracted data are provided as supplementary files.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: W.K. conceived the study, performed the literature search, data extraction and statistical analysis, and drafted the manuscript. W.H. participated in literature screening, data verification and manuscript revision. Both authors read and approved the final manuscript.

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Table 1. Characteristics of the included studies

Study	Design	Intervention vs control	Sample size	Main outcomes
Wan 2016 [5]	RCT subgroup (double-blind)	Nesiritide vs placebo	47/43	Urine output, treatment failure, CRS, death
Kelesidis 2012 [6]	Retrospective cohort	Nesiritide vs standard diuretics	328/330	GFR, hypotension, 30-day death/rehospitalization
Li Xinru 2023 [7]	Non-randomized controlled	rhBNP + amiodarone vs amiodarone	44/43	Response rate, cardiac function, inflammatory factors
Tao Shuoqiu 2018 [3]	RCT	rhBNP + conventional vs conventional	45/45	Efficacy, LVEF, NT-proBNP, endothelial function
Wang Lixia 2012 [8]	RCT (open-label)	rhBNP + conventional vs conventional	50/48	E/Em, LVMI, LAVI, 6MWD
Zhang Aiwen 2015 [9]	RCT (allocation by visit date)	rhBNP + conventional vs conventional	98/92	Response rate, E/A, BNP, CRP, 6MWD
Li Meng 2009 [1]	RCT	rhBNP + conventional vs conventional	35/30	E/A, NO, IVRT, ET-1

CRS: cardiorenal syndrome; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; E/Em: mitral early diastolic velocity/early diastolic mitral annular velocity; LVMI: left ventricular mass index; LAVI: left atrial volume index; 6MWD: 6-minute walk distance; BNP: B-type natriuretic peptide; CRP: C-reactive protein; E/A: ratio of early to late mitral inflow velocities; NO: nitric oxide; IVRT: isovolumic relaxation time; ET-1: endothelin-1.

Table 2. Summary of meta-analysis results

Outcome	Studies	Effect size	95% CI	I ² (%)	P value
Overall clinical response rate	2	OR 2.97	1.40-6.28	0	<0.01
LVEF (%)	2	MD 5.82	4.07-7.57	0	<0.001
E/A ratio	2	MD 0.27	0.21-0.33	0	<0.001
6MWD (m)	2	MD 26.56	12.98-40.13	4.6	<0.001
NT-proBNP (SMD)	2	SMD -2.49	-4.29 to -0.69	95.2	<0.01
Serum NO (μmol/L)	2	MD 11.81	0.53-23.09	91.5	0.04
IVRT (ms)	2	MD -10.94	-18.88 to -3.00	93.4	<0.01
Death or HF rehospitalization	2	OR 0.79	0.22-2.82	65.9	0.71
Worsening renal function	2	OR 1.32	0.38-4.60	74.8	0.67

MD: mean difference; SMD: standardized mean difference; OR: odds ratio; CI: confidence interval; LVEF: left ventricular ejection fraction; 6MWD: 6-minute walk distance; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NO: nitric oxide; IVRT: isovolumic relaxation time; HF: heart failure.

Figure legends

Figure 1. PRISMA 2020 flow diagram of study selection.

Figure 2. Forest plot of overall clinical response rate (OR, random-effects model).

Figure 3. Forest plot of left ventricular ejection fraction (MD, random-effects model).

Figure 4. Forest plot of E/A ratio (MD, random-effects model).

Figure 5. Forest plot of NT-proBNP (SMD, random-effects model).

Figure 6. Forest plot of 6-minute walk distance (MD, random-effects model).

Figure 7. Forest plot of serum nitric oxide (MD, random-effects model).

Figure 8. Forest plot of isovolumic relaxation time (MD, random-effects model).

Figure 9. Forest plot of death or heart failure rehospitalization (OR, random-effects model).

Figure 10. Forest plot of worsening renal function (OR, random-effects model).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryDataMetaanalysisrhBNPHFpEFBMC.xlsx](#)
- [PRISMA2020ChecklistEnglishBMC.docx](#)