

Perindopril vs Enalapril in Patients with Systolic Heart Failure: Systematic Review and Metaanalysis

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ABSTRACT

Background: Angiotensin-converting enzyme (ACE) inhibitors are highly effective at improving prognosis in a variety of disease states such as hypertension, cardiovascular disease, systolic heart failure, and acute coronary syndrome. Although these medications have been used in clinical practice for decades, not all ACE inhibitors are equal, as agents within this class vary in lipophilicity, tissue-ACE binding, antioxidant properties, antiinflammatory properties, bradykinin site selectivity, and duration of action. The objective of this systematic review and metaanalysis was to evaluate the effects of perindopril vs enalapril on left ventricular function in patients with systolic heart failure.

Methods: We conducted a systematic review and metaanalysis of trials comparing perindopril and enalapril in systolic heart failure. Relevant studies were identified through searches of MEDLINE, EMBASE, Web of Science, and Google Scholar.

Results: Three trials comparing enalapril with perindopril in 116 patients with systolic heart failure were identified.

Compared to enalapril, perindopril significantly improved cardiac sympathetic nerve activity: the pooled mean net change in heart to mediastinum ratio was 0.12 (95% confidence interval [CI]: 0.08, 0.16) and the pooled mean net change in washout rate was –3.51% (95% CI: –4.17, –2.85). Other variables also showed improvement. The pooled mean net change in New York Heart Association functional class was –0.44 (95% CI: –0.86, –0.03) and the change in brain natriuretic peptide was –64.1 [95% CI: –80.8, –47.4]. The change in left ventricular ejection fraction was not significantly greater with perindopril than enalapril: 1.15% (95% CI: –2.74, 5.04). However, in the 2 trials that switched patients from enalapril to perindopril, left ventricular ejection fraction at 6 months was significantly greater in the perindopril group: 2.41% (95% CI: 1.26, 3.55; $P < 0.0001$).

Conclusion: In patients with systolic heart failure, perindopril significantly improves cardiac sympathetic nerve activity, brain natriuretic peptide, and New York Heart Association functional class compared to enalapril. Additionally, when patients were switched from enalapril to perindopril, left ventricular ejection fraction at 6 months was significantly greater.

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INTRODUCTION

Angiotensin-converting enzyme (ACE) inhibitors are highly effective at improving prognosis in a variety of disease states such as hypertension, cardiovascular disease, systolic heart failure (HF), and acute coronary syndrome. Although these medications have been used in clinical practice for decades, not all ACE inhibitors are equal, as agents within this class vary in lipophilicity, tissue-ACE binding, antioxidant properties, antiinflammatory properties, bradykinin site selectivity, and duration of action.

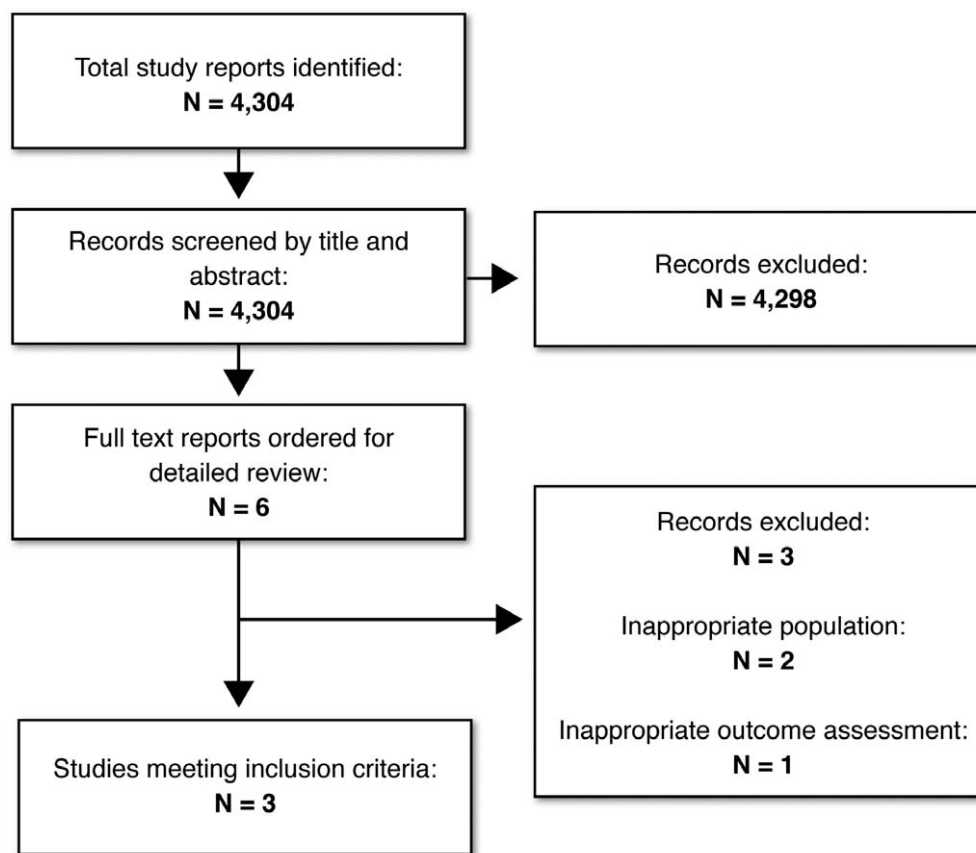


Figure 1. Process for selecting included trials.

Perindopril has a longer duration of action, stronger tissue-ACE binding, and a higher selectivity for bradykinin sites compared to many other ACE inhibitors, particularly enalapril.¹⁻⁶ Perindopril inhibits endothelial cell apoptosis, improves transforming growth factor and collagen III, and improves endothelial nitric oxide synthase protein expression and activity in the aorta significantly more than enalapril.⁷⁻⁹ Additionally, perindopril has shown better antiinflammatory, antiatherosclerotic, antioxidant, and profibrinolytic effects compared to enalapril.¹⁰ Because perindopril seems to offer pleiotropic effects that are not equally shared by enalapril, we performed a systematic review and metaanalysis of trials comparing perindopril vs enalapril in patients with systolic HF.

METHODS

Data Sources and Searches

We conducted a systematic review of the available literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for the conduct of systematic reviews of intervention studies.¹¹ We identified relevant studies through searches of MEDLINE, EMBASE, Web of Science, and Google Scholar through November 2012. To

identify further potentially relevant studies missed by the electronic database search, we manually screened reference lists from identified trials and review articles. The review was kept up to date via automated weekly email alerts.

Study Selection and Quality Assessment

The literature search and study selection were undertaken by JJD and TH using a standardized approach. All completed trials assessing enalapril vs perindopril in systolic HF patients with left ventricular ejection fraction (LVEF) <45% were eligible for inclusion.¹²⁻¹⁴ Risk of bias was assessed using criteria recommended by the Cochrane Collaboration, specifically for evaluating sequence generation of allocation; allocation concealment; blinding of participants, staff, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias.¹⁵ Trials with high or an unclear risk of bias for the first 3 criteria were considered high bias-risk trials and the rest were considered low bias-risk trials.

Data Extraction

The following data were extracted from each study: the number of patients per arm, the nature of the intervention,

Table 1. Characteristics and Quality Assessment of Each Trial

| | Masuelli et al ¹² | Tsutamoto et al ¹³ | Kasama et al ¹⁴ |
|--|--|--|---|
| Patients (n) and protocol | 31 patients on chronic (at least 6 months) enalapril (mean dose 30 mg) were switched to perindopril (mean dose 4 mg). | 45 patients in 2 groups were enrolled: group I (n=24) was on continuous enalapril treatment at a stable dose; group II (n=21) on enalapril (10 mg/d) was changed to perindopril (4 mg/d), a comparable antihypertensive dose. After randomization, in group I, enalapril treatment was continued at the same dose (8.6 ± 0.6 mg/d) and in group II, enalapril was changed to perindopril (4.9 ± 0.5 mg/d). | 40 patients with CHF (LVEF <45% [mean $33\% \pm 7\%$]) were randomly assigned to perindopril (2 mg/d; n=20) or enalapril (5 mg/d; n=20). |
| Inclusion criteria | Patients with NYHA functional class I-IV (determined by physician) who had been receiving conventional treatment and a regular stable dose of enalapril for at least the last 6 months, at the highest tolerated dose. At switch, 40% of the patients were receiving the maximum recommended dose for enalapril. | Stable CHF outpatients who had been receiving conventional therapy, including enalapril, carvedilol, and spironolactone, for more than 6 months (mean follow-up of 2.2 ± 0.15 years). | Patients were admitted with a first episode of CHF. Patients were in NYHA functional class II or III at the time of enrollment and had LVEF <45% (mean $33\% \pm 7\%$). |
| Starting and ending NYHA functional class | 2.0 vs 1.2 ($P<0.001$) Change from end of enalapril to 12 months after perindopril. | Group I (enalapril): no significant change. Group II (perindopril): significant improvement ($P<0.05$). | Patients in both groups showed improvement after 6 months of treatment compared with the baseline values (in patients receiving perindopril, $P<0.001$; in patients receiving enalapril, $P<0.05$). |
| Follow-up | Mean follow-up: 27.3 months of enalapril and 12.7 months of perindopril. | 6 months | 6 months |
| Starting and ending blood pressure, mmHg | Starting BP: 131.7/89 Ending BP: 119.3/71.5 ($P<0.001$) | In patients receiving perindopril (group II), blood pressure did not change (starting BP: 111/68; ending BP: 112/68). | No data |
| Heart failure etiology | Ischemic (n=8), postmyocarditis (n=2), congenital hypertrophic (n=2), hypertensive (n=1), radiogenic (n=1), unidentified or idiopathic (n=17). | DCM/ICM: 20% / 4% (group I, enalapril) 16% / 5% (group II, perindopril) | OMI/DCM/VD: 9% / 5% / 6% (perindopril) 10% / 6% / 4% (enalapril) |
| Quality assessment^a | ± ± - | ± ± ± | ± ± ± |

BP, blood pressure; CHF, congestive heart failure; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OMI, old myocardial infarction; VD, valvular disease.

^aRisk of bias is based on sequence generation of allocation, allocation concealment, and blinding: + represents low bias risk, - represents high bias risk, and ± represents unclear bias risk.

Table 2. Perindopril vs Enalapril in Congestive Heart Failure

| Trial | N | Results |
|--|----------|---|
| Masuelli et al¹² HF patients: mean LVEF 22.4% HF etiology: mainly ischemic (n=8) or idiopathic (n=17) Duration: 12 months | 31 | Significant improvements were seen in NYHA functional class after switching from enalapril to perindopril ($P<0.001$). Systolic and diastolic BPs were significantly decreased after the switch by 9.5 and 8.3 mmHg and 12.4 and 8.5 mmHg at 6 and 12 months, respectively ($P<0.001$). Heart rate also significantly decreased by 14 bpm at the end of perindopril treatment ($P<0.001$). LVDD and LVMI significantly decreased on perindopril (64.5 vs 61.4 mm, $P=0.001$, and 164.2 vs 143.3 g/m ² [13% decrease], $P<0.001$, respectively). After 1 year of treatment, LVEF significantly increased by 14.2%, from 22.4% on enalapril to 26.1% on perindopril ($P<0.001$). |
| Tsutamoto et al¹³ Stable, ischemic or dilated, congestive HF patients: LVEF <45% Duration: 6 months | 45 | After 6 months, perindopril significantly improved NYHA functional class, LVEF (42.6% vs 44.9%, $P=0.013$), plasma BNP (127.4 ± 32 vs 83 ± 18 pg/mL, $P=0.042$), H/M (2.0 ± 0.07 vs 2.15 ± 0.07 , $P=0.013$) and WR ($33.0\% \pm 1.4\%$ vs $30.5\% \pm 1.2\%$, $P=0.030$) compared with baseline values. Patients who were kept on enalapril did not show these benefits. |
| Kasama et al¹⁴ First episode of HF: mean LVEF 33% Baseline characteristics: OMI (n=19), DCM (n=11), VD (n=10) Duration: 6 months | 40 | Patients receiving perindopril showed significant improvement in TDS (39 ± 10 to 34 ± 9 , $P<0.01$), H/M ratio (1.62 ± 0.27 to 1.76 ± 0.29 , $P<0.01$), WR ($50\% \pm 14\%$ to $42\% \pm 14\%$, $P<0.05$), plasma BNP (226 ± 155 to 141 ± 90 pg/mL, $P<0.0005$), LVEDV (180 ± 30 to 161 ± 30 mL, $P<0.05$) and LVESV (122 ± 35 to 105 ± 36 mL, $P<0.05$). Patients randomized to enalapril did not show these benefits. |

BNP, brain natriuretic peptide; BP, blood pressure; DCM, dilated cardiomyopathy; HF, heart failure; H/M, heart to mediastinum ratio; ICM, ischemic cardiomyopathy; LVDD, left ventricular diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; NYHA, New York Heart Association; OMI, old myocardial infarction; TDS, total defect score; VD, valvular disease; WR, washout rate.

blood pressure, LVEF, HF etiology, New York Heart Association (NYHA) functional class, cardiac sympathetic nerve activity (CSNA) measured as heart to mediastinum (H/M) ratio and washout rate (WR), brain natriuretic peptide (BNP), and duration of follow-up. The data were abstracted by the 2 investigators in duplicate. Data extraction was conducted by mutual agreement and all potential disagreement was solved by another investigator (CJL).

Outcome Measures

The primary outcome of our metaanalysis was LVEF. Secondary outcomes were CSNA, BNP, and NYHA functional class. A higher H/M ratio indicates a higher myocardial uptake of ¹²³I-metaiodobenzylguanidine (MIBG), a norepinephrine analogue, that generally indicates better prognosis.¹⁶ A lower WR indicates a lower rate at which MIBG is released from the myocardium, also generally indicating better prognosis.¹⁶

Data Synthesis and Analysis

We expressed outcome results as either pooled mean net changes or mean difference (95% confidence interval [CI]). Summary estimates as well as measures of variance were computed using

DerSimonian and Laird random-effect models. The existence of heterogeneity across trials was detected by a Cochrane Q test, and the heterogeneity was quantified by an I^2 test. For I^2 statistics, $I^2<30\%$ denotes low heterogeneity, $I^2=30\%-50\%$ denotes moderate heterogeneity, and $I^2>50\%$ denotes substantial heterogeneity. Cochrane Review Manager v.5 software and Stata v.10 (StataCorp LP) were used for the analyses.

RESULTS

Identification and Selection of Studies

The literature search yielded 4,304 titles, of which 6 were reviewed in full text. Of these, 3 studies involving 116 patients were deemed eligible for inclusion (Figure 1). Table 1 summarizes the characteristics and quality assessments of the included studies. Table 2 summarizes the results of the included studies. The mean baseline LVEF was 22% in the Masuelli et al study,¹² 43% in the Tsutamoto et al study,¹³ and 33% in the Kasama et al study.¹⁴

Characteristics of Included Studies

All trials included systolic HF patients (LVEF <45%). All other medications were similar among

Table 3. Pooled Mean Net Changes in Outcomes (Perindopril vs Enalapril)

| Variable | Number of Studies | Net Change | 95% Confidence Interval |
|---|-------------------|------------|-------------------------|
| Left ventricular ejection fraction, % | 3 | 1.15 | -2.74, 5.04 |
| Heart to mediastinum ratio | 2 | 0.12 | 0.08, 0.16 |
| Washout rate, % | 2 | -3.51 | -4.17, -2.85 |
| New York Heart Association functional class | 3 | -0.44 | -0.86, -0.03 |
| Brain natriuretic peptide, mg/mL | 2 | -64.1 | -80.8, -47.4 |

patients in the 2 drug groups. The trials enrolled a median of 39 patients with a median follow-up of 8 months.

Study Outcomes

All 3 trials (n=116) reported LVEF. Although changes in LVEF were not significantly statistically different between the 2 drugs, the improvement was numerically greater with perindopril vs enalapril: 1.15% (95% CI: -2.74, 5.04). Significant heterogeneity was seen ($P=0.01$, $I^2=80.4\%$) (Table 3 and

Figure 2). When patients were switched from enalapril to perindopril (2 trials, n=76), the 6-month difference in LVEF was significant in favor of perindopril: 2.41% (95% CI: 1.26, 3.55; $P<0.0001$). No heterogeneity was seen ($I^2=0\%$) (Table 3 and Figure 3).

Two trials (n=85) measured H/M ratio. Compared to enalapril, perindopril significantly increased the H/M ratio. The pooled mean net change in the H/M ratio was 0.12 (95% CI: 0.08, 0.16). No significant heterogeneity was observed ($P=0.81$, $I^2=0\%$) (Table 3 and Figure 4).

Two trials (n=85) measured WR. Compared to enalapril, perindopril significantly decreased the WR. The pooled mean net change in WR was -3.51% (95% CI: -4.17, -2.85). No significant heterogeneity was observed ($P=0.73$, $I^2=0\%$) (Table 3 and Figure 5).

Three trials (n=116) measured NYHA functional class. Compared to enalapril, perindopril significantly improved the NYHA functional class; the pooled mean net change was -0.44 (95% CI: -0.86, -0.03). Significant heterogeneity was seen ($P=0.001$, $I^2=85.3\%$) (Table 3 and Figure 6).

Two trials (n=85) measured BNP. Compared to enalapril, perindopril significantly decreased BNP. The pooled mean net change in BNP was -64.1 (95% CI: -80.8, -47.4). No significant heterogeneity was observed ($P=0.68$, $I^2=0\%$) (Table 3 and Figure 7).

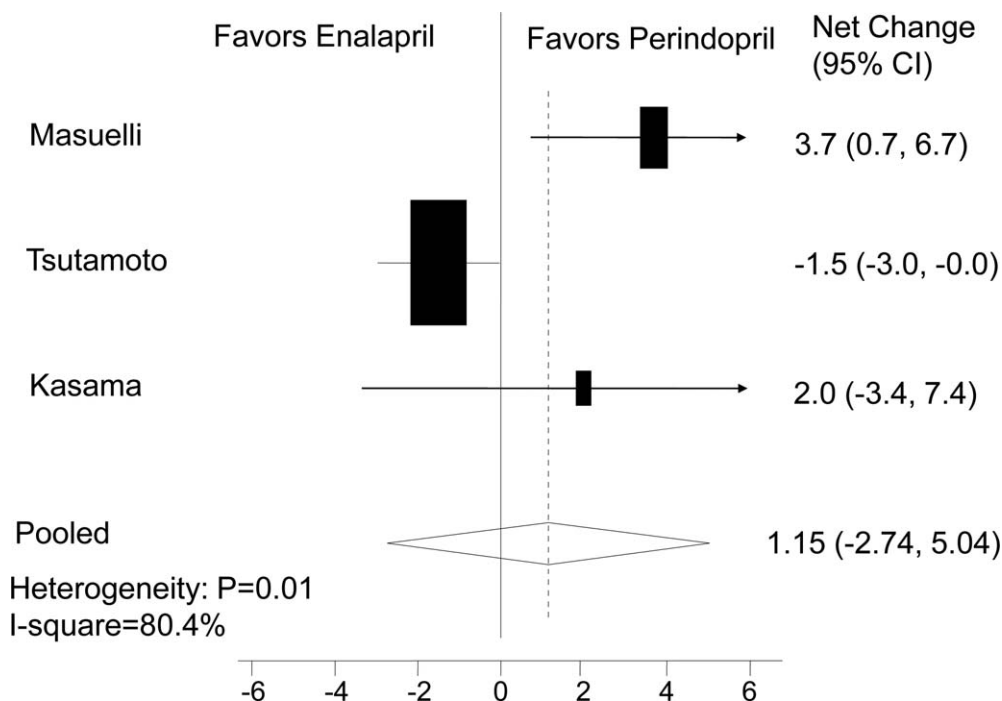


Figure 2. Forest plot of the net percentage change in left ventricular ejection fraction. CI, confidence interval.

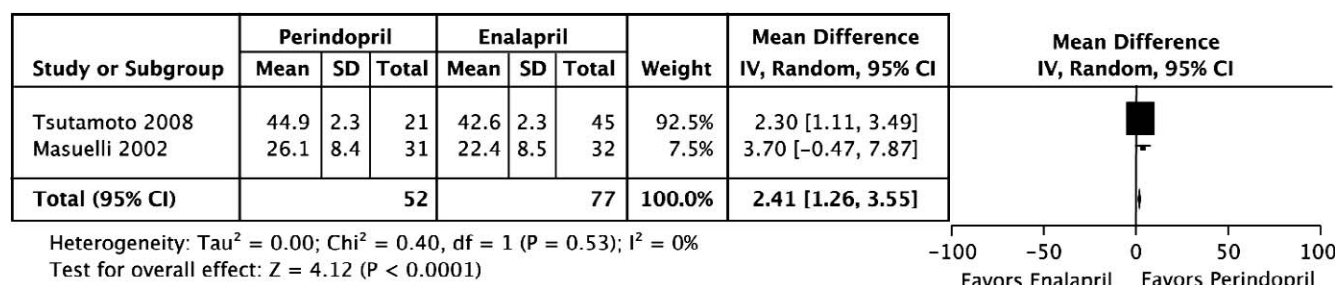


Figure 3. Forest plot of left ventricular ejection fraction at 6 months: enalapril vs perindopril. CI, confidence interval; IV, inverse variance; Random, random effects; SD, standard deviation.

DISCUSSION

This systematic review indicates that perindopril significantly improves CSNA (measured by H/M ratio and WR), BNP, and NYHA functional class compared to enalapril in patients with systolic HF (Table 3).¹²⁻¹⁴ Additionally, when patients were switched from enalapril to perindopril, LVEF at 6 months was significantly greater in the perindopril group. These benefits might be driven by the substantial pharmacological differences between these 2 agents.¹⁻¹⁰ Larger trials with longer follow-ups are required to determine if these improvements on surrogate endpoints result in improvements in hard endpoints. However, the evidence seems to indicate that patients with systolic HF

currently on enalapril may significantly benefit if switched to perindopril.

The interpretations of the results of the comparison trials included in this systematic review have some limitations. This metaanalysis included only 3 trials with 116 patients. We were unable to conduct sensitivity analysis, subgroup analysis, and tests for publication bias because of the small sample size. These trials were of relatively short duration (median of 8 months). Although doses were equivalent with respect to lowering blood pressure, both agents may have been underdosed in the setting of HF. Lastly, not all trials were randomized.

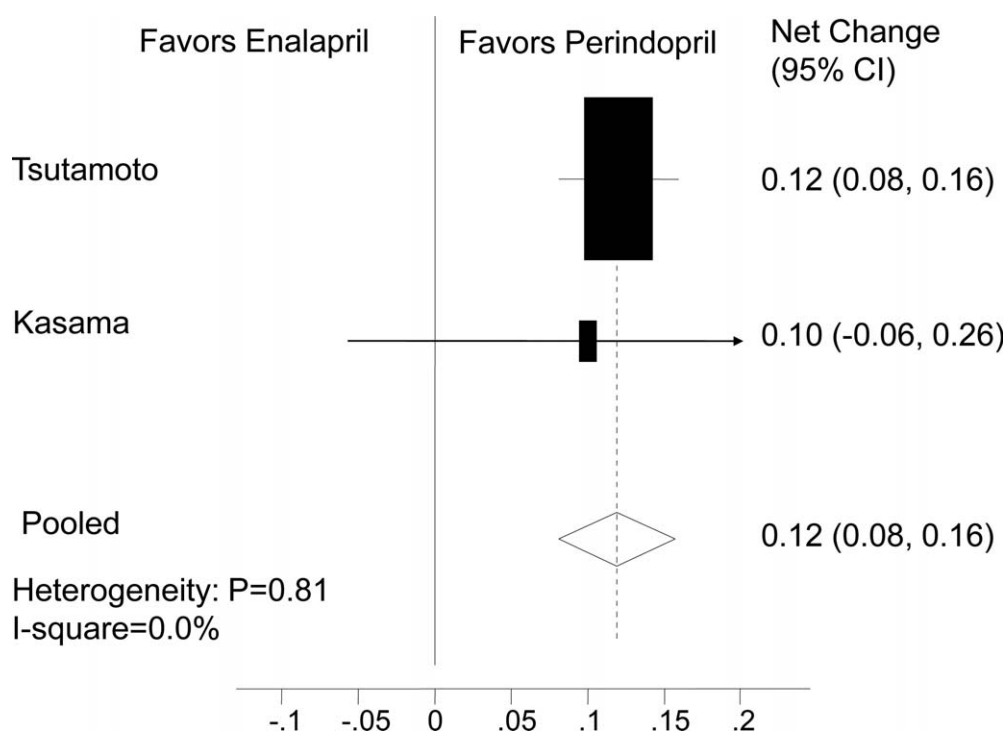


Figure 4. Forest plot of the net change in heart to mediastinum ratio. CI, confidence interval.

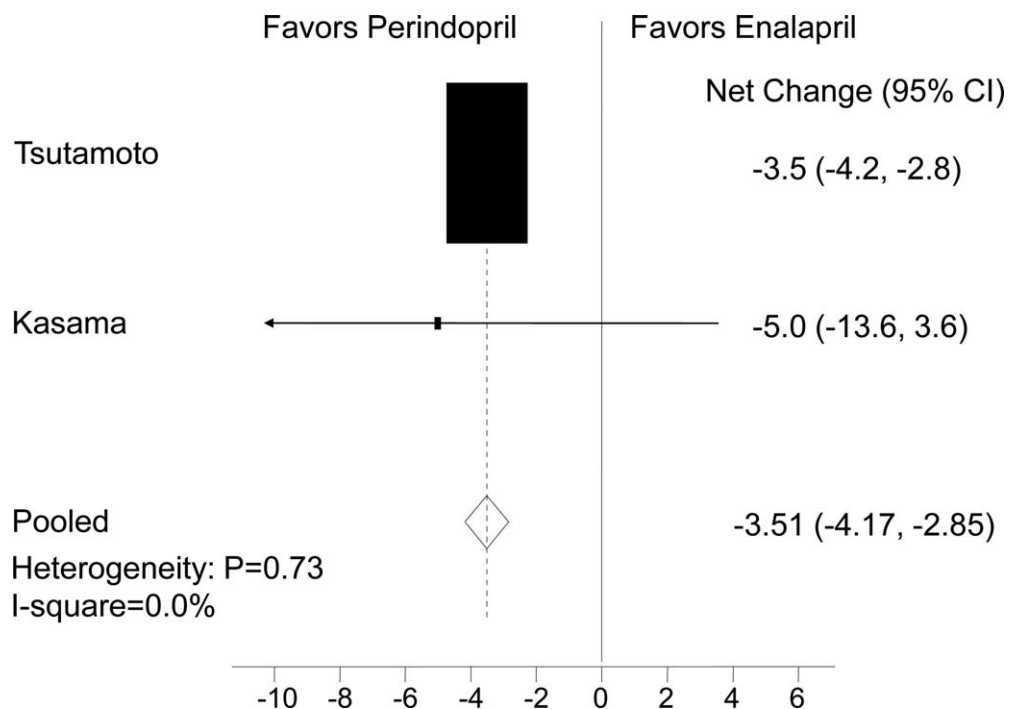


Figure 5. Forest plot of the net change in washout rate. CI, confidence interval.

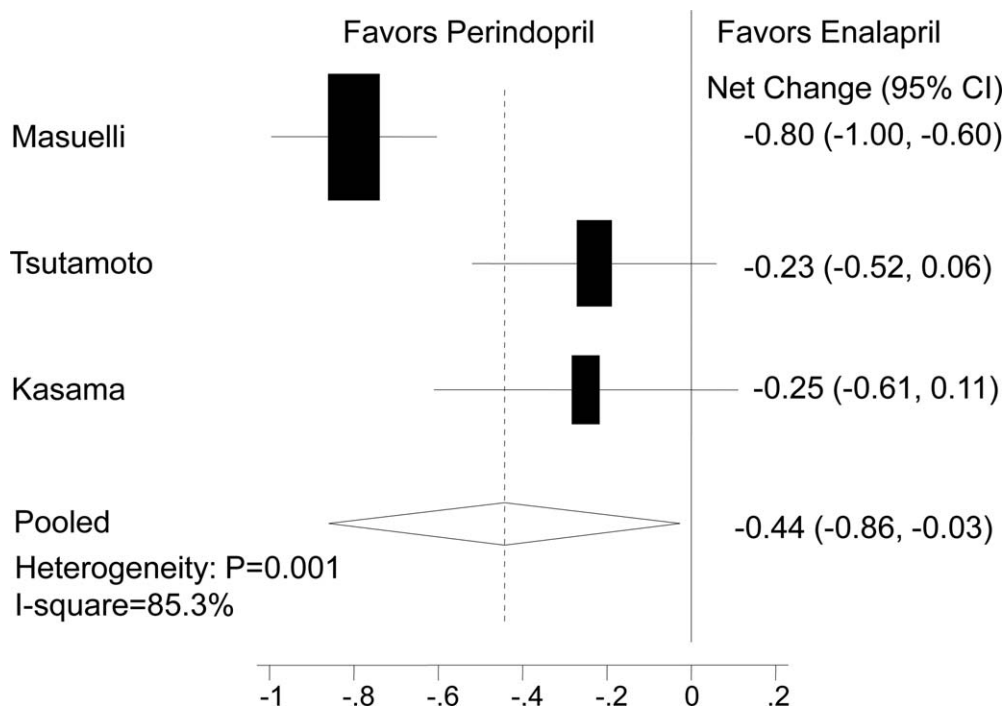


Figure 6. Forest plot of the net change in New York Heart Association functional class. CI, confidence interval.

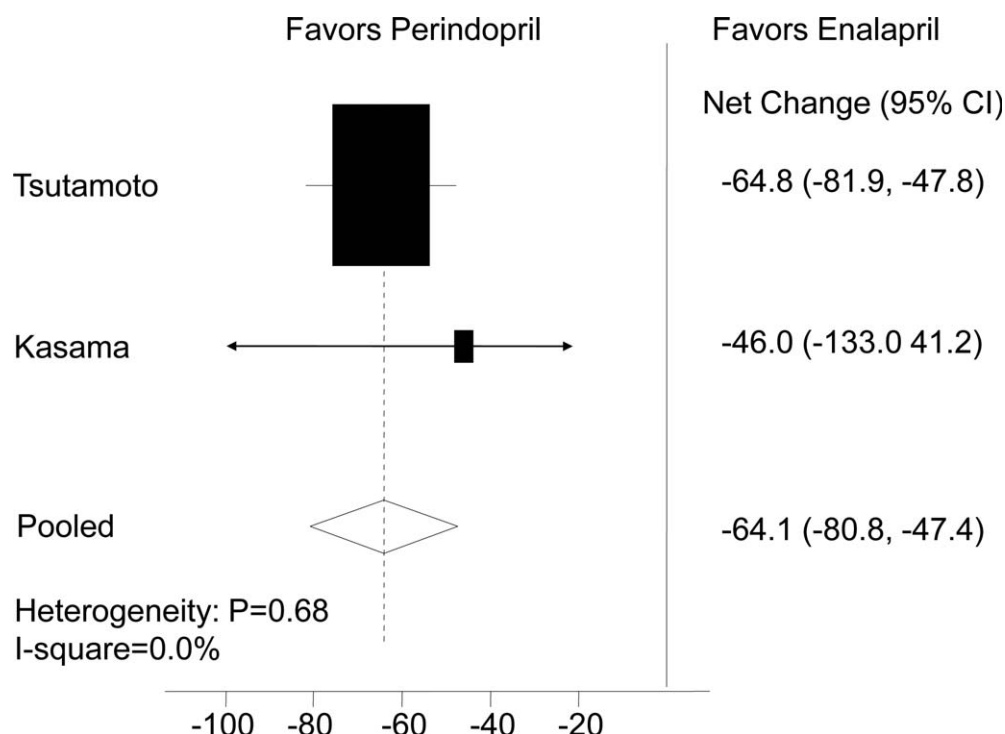


Figure 7. Forest plot of the net change in brain natriuretic peptide (pg/mL). CI, confidence interval.

However, our metaanalysis also has several strengths. We used LVEF and activation of the cardiac sympathetic nervous system, both of which are important prognostic indicators in congestive HF patients.^{17,18} Cardiac imaging with ¹²³I-MIBG is a useful tool for detecting myocardial sympathetic nerve activity abnormalities and is predictive of mortality in patients with congestive HF.¹⁹⁻²⁴ Thus, improvements in CSNA when switching from enalapril to perindopril may translate into improvements in morbidity and mortality. In an analysis of 43,316 HF patients filling prescriptions for ACE inhibitors within 30 days after hospital discharge, patients receiving enalapril and captopril had a higher risk of mortality during long-term follow-up compared to those receiving ramipril, which has greater similarity to perindopril from an overall ACE inhibitor profile (hazard ratio 1.10, 95% CI: 1.04, 1.16 and hazard ratio 1.13, 95% CI: 1.01, 1.26, respectively), and individuals receiving perindopril had an equivalent risk for mortality compared to ramipril.²⁵

CONCLUSION

Perindopril yields greater improvements in CSNA, BNP, and NYHA functional class compared to enalapril among patients with systolic HF. Large, long-term studies are warranted to confirm the apparent benefits of perindopril over enalapril (or

other similar ACE inhibitors, such as the commonly prescribed lisinopril) in patients with systolic HF. However, this type of analysis is unlikely to be performed because all ACE inhibitors are now available as generic agents; therefore, analyzing currently available data may be more important. Additionally, perindopril does not have an indication from the US Food and Drug Administration for HF although it has many other cardiovascular indications, including reduction in cardiovascular mortality. Nevertheless, perindopril's impressive track record of improving cardiovascular prognosis in large randomized controlled trials,²⁶ especially when considered in the context of the findings of this metaanalysis, provides a compelling argument for the use of perindopril as a potential first-line agent in systolic HF.

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