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A meta-analysis of the effect of angiotensin-converting enzyme inhibitors on functional capacity in patients with symptomatic left ventricular systolic dysfunction

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Abstract

Aim: To determine by meta-analysis whether angiotensin-converting enzyme (ACE) inhibitors improve exercise tolerance in patients with symptomatic left ventricular systolic dysfunction (LVSD). *Methods and results*: After literature search 13 multi-centre double blind parallel group trials that evaluated the effect of ACE inhibitors vs. placebo on exercise duration were selected. Ninety-four percent of patients were in New York Heart Association class II–IV. The studies were combined using the Cochrane meta-analysis program (Review manager version 4.1). Analyses according to treatment period, exercise protocols and publication periods were performed. Treatment with ACE inhibitor over 4–12 weeks resulted in a beneficial effect on exercise duration ($P = 0.003$ and $P = 0.0008$ for 4- and 12-weeks treatment, respectively), but the magnitude of improvements did not exceed 30 s corresponding to only 5% compared with placebo. *Conclusion*: In addition to the pronounced effect on mortality and morbidity in patients with symptomatic LVSD, ACE inhibitors have improving effect on functional capacity measured as exercise tolerance time.

Keywords: Angiotensin-converting enzyme inhibitor; Congestive heart failure; Exercise tolerance; Exercise capacity; Clinical trial

1. Introduction

Angiotensin-converting enzyme (ACE) inhibition is a cornerstone in the treatment of patients with reduced left ventricular function in either congestive heart failure or acute myocardial infarction. Many randomised studies on ACE inhibitors demonstrate a clear reduction in mortality and hospitalisation for patients with heart failure [1–4]. Compared to these results, data on the other endpoints such as functional capacity are much less clear. The available data on the functional capacity measured by exercise tolerance are conflicting. In 1996 Narang et al. reviewed 35 randomised studies evaluating the effect of ACE inhibitors on functional capacity and found that ACE inhibitors had a beneficial effect on exercise tolerance time and New York Heart Association (NYHA) classification [5]. It is therefore commonly stated that ACE inhibitors improve functional capacity, symptoms and prognosis. Since Narang's review several studies have been published showing no significant beneficial effect on exercise tolerance [6–9]. Therefore, we found it important to perform a meta-analysis of studies evaluating exercise tolerance to determine whether these agents produce any beneficial effect on this variable. It is important to clarify these aspects in order to establish reasonable recommendations, as patients are likely to discontinue long-term therapy if they do not feel relevant functional improvement.

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2. Methods

2.1. Search strategy

We searched medical literature through MEDLINE and EMBASE for all clinical trials on ACE inhibitors using the following keywords: angiotensin-converting enzyme inhibitor, congestive heart failure, exercise tolerance, exercise capacity, clinical trial and human, without time limitation. Additionally, a manual search was conducted using all previous reviews, and meta-analyses on ACE inhibitors. The Cochrane database showed no meta-analysis concerning this subject.

2.2. Criteria and selection of the studies

All randomised controlled studies comparing ACE inhibitors vs. placebo and high vs. low dose of ACE inhibitors on patients with clinically established diagnosis of congestive heart failure with left ventricular dysfunction and concurrently having performed an exercise tolerance test (bicycle ergometer, treadmill, 6-min walk) before and after a certain therapy period, were considered eligible to inclusion into the meta-analysis. A total of 49 studies [6–55] were identified, one study on exclusively non-symptomatic patients [56] and one withdrawal study [57] was excluded to minimize bias. Two previously published meta-analysis including six unpublished studies were also identified [58,59].

The outcome measure was exercise duration because this was the common measured variable in all studies. The reported data on peak oxygen consumption [14,24,26–28] and 6-min walk test [13,14] were heterogeneous and insufficient; and accordingly were not meta-analysed.

The authors and pharmaceutical companies responsible for a number of published studies with insufficient presentation of results and for unpublished studies were contacted, but the authors were unable to provide any data- either because the data were destroyed, not available, or because no replies were given. Consequently, 20 published studies [6,10,38–55] and the six unpublished studies included in the previous meta-analysis [58,59] also had to be excluded. The reason of exclusion in six studies [6,42–44,53,55] was unreported standard deviations, in 13 studies [38–41,45–52] both exercise duration and its standard deviations were unreported, and one study did not precisely report the number of patients in each group [10]. The total excluded population at the end of these 20 studies was 1544 patients. Thus, out of the 49 published studies only 29 studies were retained. Further 11 studies evaluating the effect of ACE inhibitor vs. placebo [11,17–27], three studies evaluating 1-year treatment [9,28,30], and two studies evaluating low vs. high dose without placebo arm [36,37] were also excluded. These 16 studies were characterised by small populations (<50 patient, the vast majority included 10–30 patients) and had a wide range of confidence interval for effect size inducing significant heterogeneity ($P=0.0009$) together with the large multi-centre studies and possible publication bias (Fig. 1). Therefore, only 13 studies were selected for a meta-analysis of the effect of ACE inhibitors vs. placebo on exercise tolerance time and consequently no eligible data were left to analyse 1-year effect or the high vs. low dose comparison.

Because of missing information on allocation concealment it was not possible to score for study quality properly. However, these 13 studies were large multi-centre double blind parallel group trials [7,8,12–16,29,31–35] wherein the allocation concealment might be considered adequate.

2.3. Data analysis

In the studies using two different ACE inhibitors or exercise protocol in two separate arms, each ACE inhibitor or protocol arm was compared independently with placebo [7,12,13]. In the studies comparing different doses of the same ACE inhibitor vs. placebo, the mean result of the ACE inhibitor arms was analysed together with the results of the other studies vs. placebo [7,8,14,15]. The analysis was based on the data provided by the number of patients at the end of each treatment period.

Cochrane Collaboration, Nordic Cochrane Centre's meta-analysis program called Review Manager (Rev Man version 4.1) was used [60]. This program allows selection of different meta-analytic methods. Chi-square method tests homogeneity of studies and Z score tests the overall probability of results. Funnel plots can be made to detect publication bias.

Exercise durations at the end of 4- and 12-weeks treatment were compared between ACE inhibitor and control groups. We chose the random-effects model for continuous data, which provides the weighted mean difference with 95% confidence interval. All values presented as standard error of mean in the original studies [29,31,34] were recalculated to their standard deviations. In case of

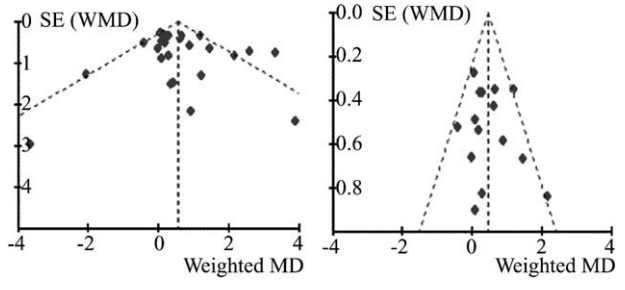

Fig. 1. Funnel plots of the 12-weeks studies with (left) and without (right) the small sample studies. The plot to the left shows the small studies spread widely from the mean effect line (punctured midline) and some of them are out of the 95% confidence interval lines (punctured tent-shaped line) because of their large random error in contrast to the large multi-centre studies that are distributed almost normally within the confidence interval limits (right). This skewed distribution of the small studies was associated with significant heterogeneity ($P=0.0009$) and indicated possible publication bias. In these plots the treatment effects (WMD = weighted mean difference) are plotted against their standard error (S.E.).

unreported standard deviations in the post-treatment values the pre-treatment values were substituted [7,8,12,30]. The results of exercise durations in minutes were expressed as means and standard deviations. Z score <2 and P-values >0.05 were considered insignificant.

3. Results

Characteristics of the selected studies and populations are shown in Tables 1 and 2. Left ventricular systolic dysfunction (LVSD) was reported as reduced ejection fraction or

Table 1
Characteristics of the 13 double blind multi-centre studies included in the meta-analysis

No.	Study or author name and publication year	ACEI and dose	Concomitant drugs	Duration of treatment (weeks) exercise protocol	Population			
					Baseline		End	
					ACEI	*P*	ACEI	*P*
1	Cannon [16] 1983	Captopril 25–50 mg × 3	Digoxin Diuretic	12-TM	49	42	45	28
2	Zwehl [12] 1990	Lisinopril 10–20 mg × 1	Digoxin Diuretic	4-12-TM/BE	183	92		
				4-TM			81	41
				12-TM			86	42
				4-BE			73	34
				12-BE			78	40
3	Colfer [29] 1992	Benazepril 2–20 mg × 1	Digoxin Diuretic	12-TM	114	58	98	35
4	Dossegger [31] 1993	Cilazapril 5 mg × 1	Digoxin Diuretic	12-BE	72	35	63	30
5	Gundersen [32] 1994	Ramipril 10 mg × 1	Digoxin Diuretic Nitrate	12-BE	115	108	104	91
6	Brown [33] 1995	Fosinopril 10–20 mg × 1	Diuretic	4-12-TM	116	125		
				4-TM			107	110
				12 TM			90	83
7	CCMG [13a] 1995	Cilazapril 2.5–5 mg × 1	Digoxin	12- BE	221	114	191	87
		Captopril 25–50 mg × 3	Diuretic		108	114	88	87
8	FEST [34b] 1995	Fosinopril 20–40 mg × 1	Digoxin Diuretic Nitrate	4-12-BE	155	153		
				4-BE			131	132
				12-BE			127	118
9	Circo 1995 [14]	Delapril 7.5, 15, 30 mg × 2	Digoxin Diuretic	8-BE	67	34	66	27
10	CASSIS [7c] 1995	Spirapil 1.5, 3, 6 mg × 1	Digoxin Diuretic Nitrate	12-BE	248	48	110	28
		Enalapril 5–10 mg × 1	Calcium antagonist Antiarrythmic Aspirin		48	48	32	28
11	Larsen [8] 1996	Cilazapril 0.5, 1, 2.5 mg × 1	Digoxin Diuretic	12-BE	135	41	73	32
12	Veldhuisen [15] 1998	Imidapril 2.5, 5, 10 mg × 1	Digoxin Diuretic Nitrate Aspirin	12-BE	244	62	148	54
13	TRACE [35d] 2002	Trandolapril 1–4 mg × 1	Digoxin Diuretic Betablocker Calcium antagonist Thrombolytic	4-12-BE	128	126		
				4-BE			128	126
				12-BE			112	107

All studies included patients with chronic heart failure except TRACE study, whose patients performed the first exercise test 1 month after acute myocardial infarction.

ACEI = angiotensin converting enzyme inhibitor, *P* = placebo, TM = treadmill, BE = bicycle ergometer.

[a] The Cilazapril-Captopril Multicenter Group (CCMG).

[b] Fosinopril Efficacy/Safety Trial (FEST).

[c] Czech and Slovak Spirapril Intervention Study (CASSIS).

[d] TRAndolapril in Cardiac Evaluation Study (TRACE).

Table 2
Basic characteristics of the patients included in the meta-analysis. The values are presented either as range or percent of patients

Characteristic	Value
Mean age (years)	55–67
Sex (male%)	63–96
Aetiology of heart failure[*]	
Ischaemic heart disease	60%
Primary dilated cardiomyopathy	27%
Valvular heart disease	4%
Hypertension	9%
Duration of heart failure	1 month–4 years
NYHA class[**]	
I	6%
II	50%
III	40%
IV	4%

* Available in all but three studies [9,35,36].
** Available in all but one study [16].

fractional shortening in all studies. Number of participants and values of exercise durations at the end of 4- and 12-weeks treatment are shown in Figs. 2–4. Several studies contributed to both 4- and 12-weeks analysis [12,33–35] (Figs. 2–4).

Meta-analysis of five short-term (4–8 weeks) studies showed a significant benefit favouring ACE inhibitor arm with a mean difference of 0.50 (0.17–0.83) min (=30 s) in exercise duration—corresponding to an improvement of 5% (0.5–10%) (Fig. 2).

Meta-analysis of the 12-weeks studies showed a significant benefit favouring ACE inhibitor arm with a mean difference of 0.47 (0.19–0.75) min (=28 s) corresponding to an improvement of 5% (2–9%) (Fig. 3). The studies showed homogenous effects and the funnel plot showed rather symmetric and almost normal distribution (Fig. 1). A meta-analysis of 9 of 12-weeks studies using bicycle ergometer protocol showed a significant benefit with a mean difference of 0.44 (0.19–0.69) min (=26 s)—corresponding to an improvement of only 5% (2–8%) (Fig. 4).

A comparative analysis was done to show the difference in results between studies conducted before and after Narang's review. There was a significant effect of ACE inhibitors in the seven studies [12,13,16,29,31–33] published between 1983 and 1995 with a mean difference of 0.58 (0.18–1.98) min (=35 s), $P=0.005$. The five studies [7,8,14,15,34,35] published thereafter between 1996 and 2002 showed no significant effect with a mean difference of 0.37(0.003–0.76) min (=22 s), $P=0.07$. Funnel plots showed possible publication bias in both periods.

All analyses were also tested with fixed-effects model, but the change in the mean differences compared to random-effects model was slight, 1–2 s in each analysis. Despite inclusion of the previously mentioned excluded small sample studies in the above-mentioned analyses, the maximal increase in exercise tolerance time did not exceed 40 s.

4. Discussion

This meta-analysis was the result of a comprehensive data review of many studies evaluating the effect of ACE inhibitors on exercise tolerance in patients with LVSD. The results showed a statistically significant effect favouring ACE inhibitors demonstrated by prolonged mean exercise duration compared with placebo during the 4–12 weeks of treatment. The overall improvement in the magnitude of exercise duration of 30 s corresponding to 5% of the total exercise duration was small compared to that effect of ACE inhibitors on mortality and hospitalisation [1–4]. However, the results should be interpreted cautiously as this meta-analysis depended upon analysis of only one exercise tolerance parameter.

4.1. Confounding factors

Several confounding factors have been argued to influence the results of the controlled studies evaluating

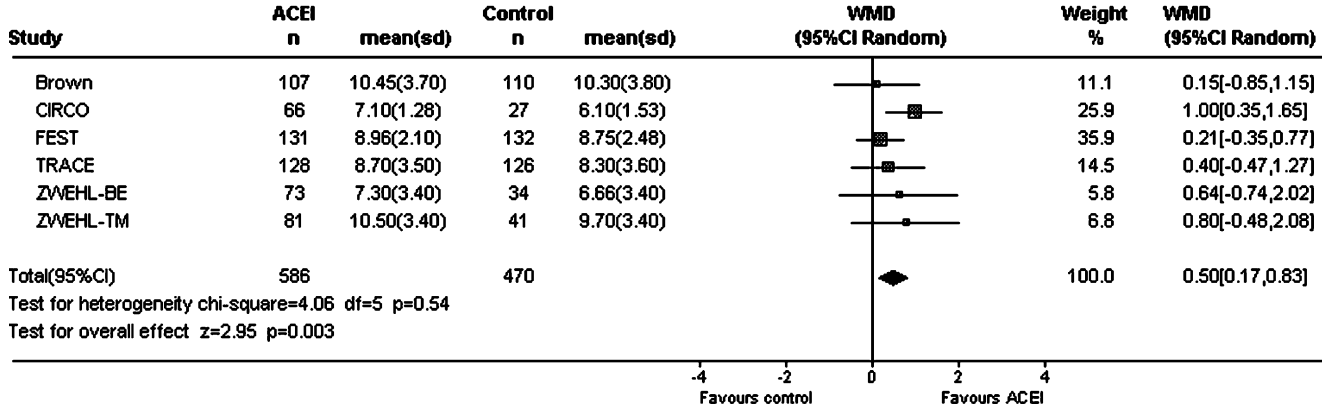

Fig. 2. Meta-analysis of five short-term (4–8-weeks) studies showed a significant effect on exercise duration with an improvement of 0.5 min (=30 s) corresponding to only 5% favouring angiotensin-converting enzyme inhibitor (ACEI). WMD=weighted mean difference, n=number, s.d.=standard deviation, CI=confidence interval.

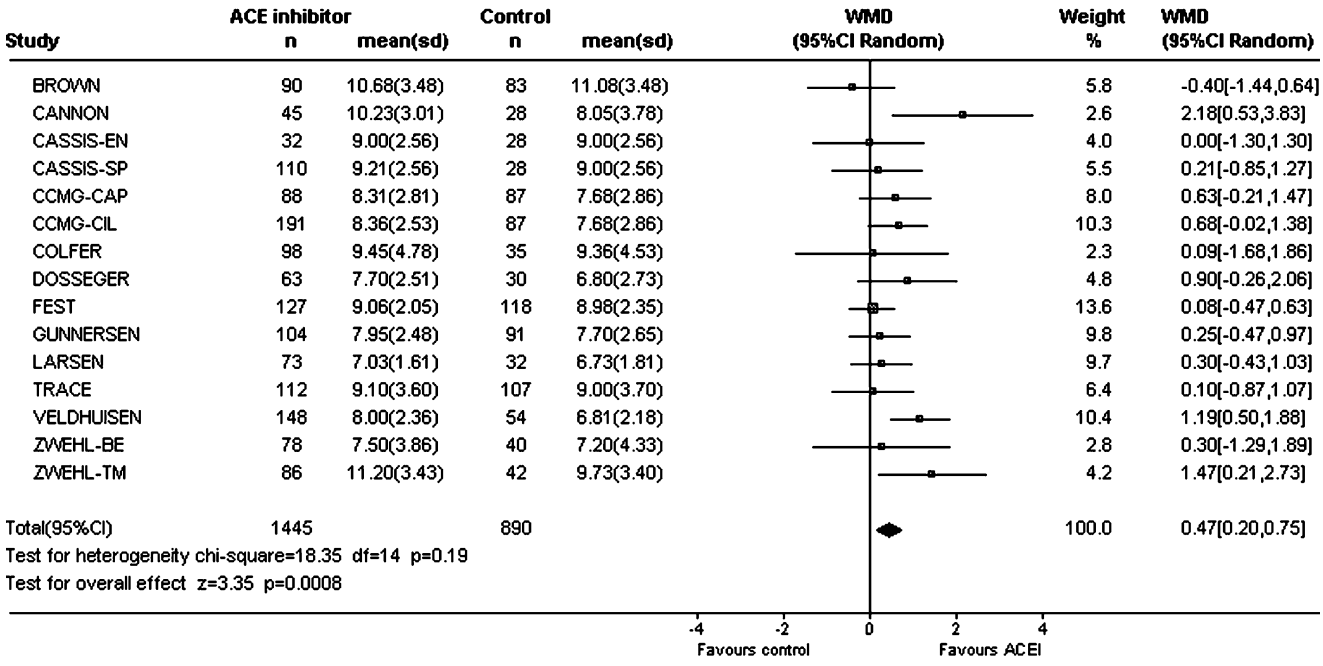

Fig. 3. Meta-analysis of the12-weeks multi-centre studies showed a significant effect on exercise time with an improvement of 0.47 min (28 s) corresponding to only 5% favouring angiotensin-converting enzyme inhibitor (ACEI). WMD = weighted mean difference, *n* = number, s.d. = standard deviation, CI = confidence interval.

exercise tolerance in patients with symptomatic LVSD. An important factor to be mentioned is the outcome of withdrawals—a problem that could be more evident in the studies with longer follow-up. Obviously, this might be due to comparatively higher mortality rate in the placebo arm and probably as a result of more frequent side effects in the ACE inhibitor arm. The lack of improvement in the ACE inhibitor arm has been partly attributed to higher mortality rates in placebo patients and with the assumption that dead patients might have been in worse clinical condition accordingly could have produced worse functional capacity. Hence, the maximal exercise tolerance time was chosen as a primary endpoint rather than mortality in these studies, the dead patients were unable to provide results of the final exercise tolerance tests. An analysis based on data of patients who ended the study would, therefore, provide clinically relevant results as no analysis can accurately account for the missed data

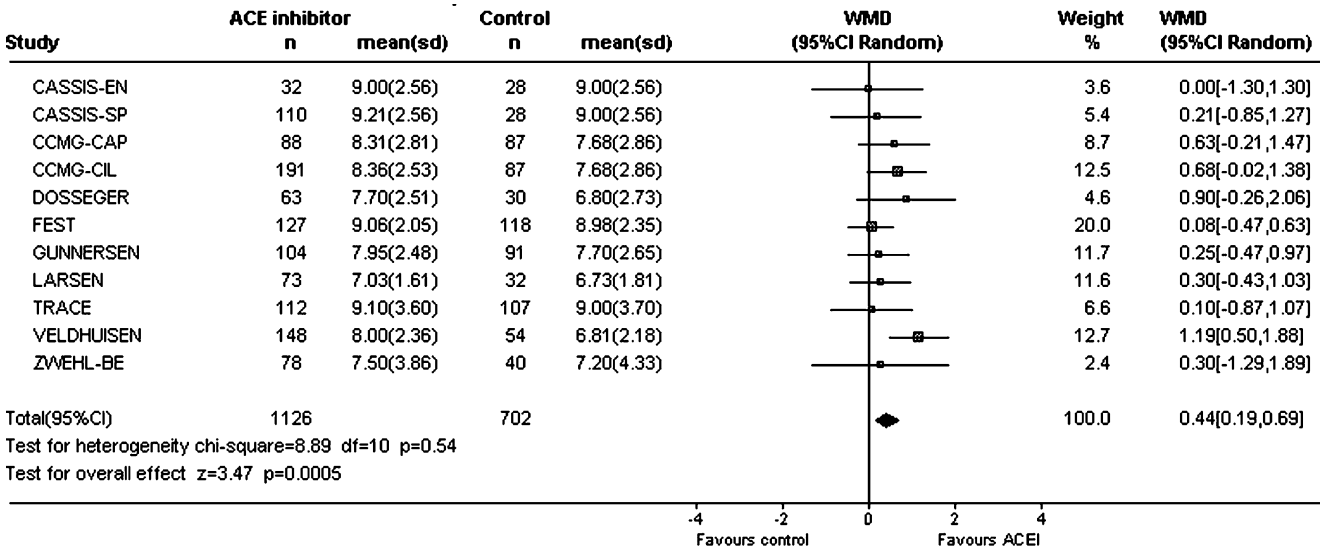

Fig. 4. Results of the meta-analysis of 9 of 12 weeks multi-centre studies that used bicycle ergometer showed significant improvement in exercise duration of 0.44 min (=26 s) corresponding to only 5% favouring angiotensin-converting enzyme inhibitor (ACEI). WMD = weighted mean difference, *n* = number, s.d. = standard deviation, CI = confidence interval.

concerning the dead patients. Inclusion of all dropouts—inclusive deaths—in an analysis on basis of intention-to-treat with an assumption that dying patients would have provided low response values—least or zero exercise duration—has been suggested [59]. In this case, the investigator has to combine data of two different end-points, which would be confusing and clinically unrealistic. The results are subjected to attrition bias but apparently this is unavoidable.

The other factor is patients' NYHA class. NYHA class may worsen due to deterioration of heart failure or improve as a result of adjustment of the concomitant therapy. Such changes in NYHA class can affect exercise performance. Generally the studies reported improvement in functional capacity, reported also improvement in NYHA class [5]. However, it could be difficult to perform exercise tests in patients with severe heart failure with NYHA class IV; subsequently these patients are prone to be unqualified to enter exercise studies or eventually become withdrawn during the course of the trial. It is also unlikely to obtain noticeable changes in exercise duration in asymptomatic patients with NYHA class I. Overall, a meta-analysis of such population is prone to some selection and performance biases. However, in this meta-analysis only a minority of the included populations were in NYHA class I or IV, 6% and 4%, respectively.

Another factor that could have affected the results is the use of concomitant medications, particularly diuretics. Only five studies took into account the effect of concomitant diuretic consumption on the exercise tolerance test [18,31,34,36,37]. However, the TRACE study has analysed this problem in details and showed that the placebo arm consumed slightly more furosemide dose (mean 12 mg/day), but this small difference could not explain the similar slight improvements in exercise duration and NYHA classes in both study arms [61].

Several studies [14,17,36] used repeated baseline exercise tests which probably added further performance bias as the investigators perhaps tried to encourage patients to reach maximal capacity to be enrolled; this bias even increases if the same investigator tests the same patient during the study. It can also be argued that repeated exercise tests might reduce variability and introduce a training effect, but attempting to exclude patients with variable exercise times could impair the results.

Methodological problems during exercise protocols may affect the results and its interpretation. Exercise protocols are usually graded; patients may manage one grade but suddenly fail to continue the test when the grade increases. Thus, the difference in magnitude of the performed exercise duration (30 s in this study) crossing a grade could be significantly large, however, the same magnitude at the same grade could be small. Using different exercise protocols seems not to be an important factor affecting the results and the general guidelines recommend individualising the choice of different exercise tests [62].

Finally, various ACE inhibitors could have exerted different effects but there is consensus on that ACE inhibitors have a class effect, thereby different effects are unexpected.

These above-mentioned factors elucidate how difficult it is to perform an ideal exercise study in patients with LVSD.

4.2. Study design and duration

It has previously been suggested that parallel studies designed for 12-weeks period would be reasonable to minimize the effect of some of the above-mentioned confounding factors. Hence, the majority of the studies included in this meta-analysis were parallel and designed for 12-weeks periods. Nevertheless it is still arguable whether 12-weeks period is adequate to make such a conclusion, because the question of maintainability of the effectiveness of ACE inhibitors in the longer term will still not be answered. Although only few studies evaluated exercise tolerance time in 1 year, the results showed no significant effect in all studies, indicating that the effectiveness of ACE inhibitors more likely diminishes and perhaps disappears in the longer terms or the mortality effect becomes more pronounced [9,28,30,35].

4.3. Homogeneity between studies

Some differences between the included studies might have caused heterogeneity and presumably might have affected the results. Using different types of ACE inhibitors or exercise protocols and NYHA class as possible sources of heterogeneity had already been discussed. Other sources of heterogeneity could be attributed to some dissimilarity in the aetiology or duration of the heart failure in the baseline population, however, in this meta-analysis all studies included patients with chronic heart failure except TRACE study whose patients performed the first exercise test 1 month after acute myocardial infarction. Additionally, the included studies were published over 20 years wherein the management of patients with LVSD and myocardial infarction progressed rapidly and might probably have led to some significant differences in concomitant therapy particularly between the earlier and later studies. Nevertheless, ACE inhibition has been the primary choice of treatment in all settings of LVSD since the large mortality studies were published. There is no evidence confirming that the effect of ACE inhibitors should be different due to the aetiology or duration of heart failure. Thus, it is unlikely that these differences between the studies could have created considerable heterogeneity.

4.4. Previous meta-analyses

Two previous meta-analyses have also evaluated the effect of ACE inhibitors on exercise duration in patients

with congestive heart failure [58,59]. Lubsen et al. [59] performed a meta-analysis on five studies ($n = 1095$) using ramipril. The studies independently showed no significant effect but the combined data showed a significant effect favouring the ramipril arm but with only 3.5% improvement compared with placebo (P-value < 0.05). Another meta-analysis performed by Kiowski et al. [58] included six studies using cilazapril ($n = 1030$); four studies independently showed no effect but the combined data showed a significant effect. The results of these two meta-analyses were limited only to a number of trials using two ACE inhibitors and they could not confirm a marked effect.

5. Conclusion

The current meta-analysis included major double blind multi-centre trials; there was a beneficial effect of ACE inhibitors on exercise duration, but this effect appears to be modest compared to the well-documented reducing effect on mortality and hospitalisation in patients with LVSD. We conclude that these patients could by receiving ACE inhibitors improve their functional capacity in addition to the well-documented effect on mortality and hospitalisation. The general guidelines for treatment of these patients should take this point into consideration.

6. Limitations of the results

This meta-analysis depended upon the available data extracted from the published studies and the efforts we made to collect the unpublished data were not successful. Consequently, a significant number of studies were unfortunately excluded leading to publication bias. There was neither sufficient data on the other exercise tolerance parameters like peak oxygen consumption to support further the analysis on exercise duration. The comparative analyses made according to publication periods also suggested significant difference between the results before and after 1996 indicating possible publication bias towards unpublished papers with negative results before 1996 and unpublished positive results thereafter. The role of confounding factors and their contribution to further bias is discussed above. The overall influence of bias particularly on short-term analysis is perhaps significant.

References

[1] The CONSENSUS Trial Study Group. Effect of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429–35.

[2] The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.

[3] Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Cuddy TE, et al. On behalf of SAVE investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. N Engl J Med 1992;327:669–77.

[4] Køber L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, et al. For the Trandoplapril Cardiac Evaluation (TRACE) Study Group. A clinical Trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1995; 333:1670–6.

[5] Narang R, Swedberg K, Clenland JGF. What is the ideal study design for evaluation of treatment for heart failure? Eur Heart J 1996; 17:120–34.

[6] Hampton JR, Cowley AJ, Wnuk-Wojnar AM. Failure of an ACE inhibitor to improve exercise tolerance. Eur Heart J 1998;19:1823–8 for the Trandolapril Study Group.

[7] Widimsky J, Kremer HJ, Jerie P, Uhlir O. Czech and Slovak Spirapril Intervention Study (CASSIS), a randomised, placebo and active-controlled, double-blind multi-centre trial in patients with congestive heart failure. Eur J Clin Pharmacol 1995;49:95–102.

[8] Larsen J, Sykulski R, Jensen G, Dossgger L, Trimarco B, Mocetti T, et al. Adaptive changes in the acute haemodynamic effects of cilazapril during chronic treatment. Eur J Clin Pharmacol 1996;50: 433–41.

[9] Patten RD, Kronenberg MW, Benedict CR, Udelson JA, Kinan D, Stewart D, et al. Acute and long-term effects of the angiotensin-converting enzyme inhibitor, enalapril, on adrenergic activity and sensitivity during exercise in patients with left ventricular systolic dysfunction. Am Heart J 1997;134:37–43.

[10] Enalapril Congestive Heart Failure Investigators. Long-term effects of enalapril in patients with congestive heart failure: a multicenter, placebo-controlled trial. Heart Failure 1987 June–July;134:102–7.

[11] Lechat P, Garnham SP, Desche P, Bounhoure JP. Efficacy and acceptability of perindopril in mild to moderate chronic congestive heart failure. Am Heart J 1993;126:796–806.

[12] Zwehl W, Rucinska E. Long-term effects of lisinopril in patients with chronic heart failure: a multicenter, placebo-controlled trial. In: Nicholls MG, editor. A focus on the clinical effects of long-acting ACE inhibitors in heart failure126. New York: Raven Press, 1990. pp. 31–40.

[13] The Cilazapril-Captopril Multicenter Group. Comparison of the effects of cilazapril and captopril vs. placebo on exercise testing in chronic heart failure patients: a double-blind, randomized, multicenter trial. Cardiology 1995;86(Suppl 1):34–40.

[14] Circo A, Platanio F, Mangiameli S, Putignano E. Multicenter, randomised, placebo-controlled, double-blind study of the safety and efficacy of oral delapril in patients with congestive heart failure. Am J Cardiol 1995;75:18F–24F.

[15] Veldhuisen DJV, Genth-Zotz S, Brouwer J, Boomsma F, et al. High vs. low-dose ACE inhibition in chronic heart failure: a double-blind placebo controlled study of imidapril. JACC 1998;32:1811–8.

[16] Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. JACC 1983;2:755–63.

[17] Sharpe DN, Murphy J, Coxon R, Hannan SF. Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study. Circulation 1984;70:271–8.

[18] Cleland JGF, Dargie HJ, Hodsman GP, Robertson JIS, et al. Captopril in heart failure. Br Heart J 1984;52:530–5.

[19] Chrysant SG, Gollup S, Dunn MI, Bal IS, et al. Hemodynamic and metabolic effects of enalapril in patients with heart failure. Clin Cardiol 1985;8:585–90.

[20] Franciosa JA, Wilen MM, Jordan RA. Effects of enalapril, a new

angiotensin-converting enzyme inhibitor, in a controlled trial in heart failure. JACC 1985;5:101–7.
[21] McGrath B, Arnolda L, Mathews PG, Jackson B, Jennings G, et al. Controlled trail of enalapril in congestive cardiac failure. Br Heart J 1985;54:405–14.
[22] Cleland JGF, Dargie HJ, Bal SG, Gillen G, et al. Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state. Br Heart J 1985; 54:305–12.
[23] McGrath BP, Arnolda LF. Enalapril reduces the catecholamines response to exercise in patients with heart failure. Eur Clin Pharmacol 1986;30:485–7.
[24] Jessup M, Spielman S, Hare T, Ulrich S, Samaha J. Lisinopril in the treatment of chronic cardiac failure: a controlled trial. Heart Failure 1987 June–July;30:114–27.
[25] Drexler H, Banhardt U, Meinertz T, Wollschlager H, et al. Contrasting peripheral short-term and long-term effects of converting enzyme inhibition in patients with congestive heart failure. Circulation 1989;79:491–502.
[26] Mulligan IP, Fraser AG, Lewis MJ, Henderson AH. Effects of enalapril on myocardial noradrenaline overflow during exercise in patients with chronic heart failure. Br Heart J 1989;61:23–8.
[27] Cochieri M, Alunni GF, Del F, Fortunati F, et al. Comparative effects of Ibopamine and captopril in mild congestive heart failure. Cardiology 1990;77:36–42.
[28] Dickstein K, Barvik S, Aarsland T. Effect of long-term enalapril therapy on cardiopulmonary exercise performance in men with mild heart failure and previous myocardial infarction. JACC 1991;18: 596–602.
[29] Colfer HT, Ribner HS, Gradman A, Hughes CV, et al. Effects of once-daily benazepril therapy on exercise tolerance and manifestations of chronic congestive heart failure. Am J Cardiol 1992;70: 354–8.
[30] Keren G, Pardes A, Eschar Y, Hansch E, et al. Left ventricular dynamics by Doppler echocardiography in dilated cardiomyopathy: 1-year follow-up in patients treated with captopril compared to placebo. Cardiology 1992;81:196–206.
[31] Dossegger L, Aldor E, Baird MG, Braun S, et al. Influence of angiotensin converting enzyme inhibition on exercise performance and clinical symptoms in chronic heart failure: a multicentre, double-blind, placebo-controlled trial. Eur Heart J 1993;14(Supp C): 18–23.
[32] Gunnersen T, Swedberg K, Amtorp O, Remes J, Nilsson B. Absence of effect on exercise capacity of 12-week treatment with ramipril in patients with moderate congestive heart failure. Eur Heart J 1994;15:1659–65 on behalf of The Ramipril Study Group.
[33] Brwon EJ, Chew PH, Maclean A, Gelperin K, et al. Effects of fosinopril on exercise tolerance and clinical deterioration in patients with chronic congestive heart failure. Am J Cardiol 1995;75:596–600.
[34] Erhardt L, Maclean A, Ilgenfritz J, Gelperin K, Blumenthal M. Fosinopril attenuates clinical deterioration and improves exercise tolerance in patients with heart failure. Eur Heart J 1995;16: 1892–9.
[35] Abdulla J, Torp-Pedersen C, Abildstrøm SZ, Køber L. The effect of angiotensin-converting enzyme inhibitor Trandolapril on exercise tolerance time in patients with left ventricular dysfunction. JACC 2002;39(Suppl. A):148A.
[36] Brunner-La Rocca HP, Weillenmann D, Kiowski W, Maly FE, et al. Within-patients comparison of different dosages of enalapril on functional capacity and neurohormaonl levels in patients with chronic heart failure. Am Heart J 1999;138:654–62.
[37] Tang WHW, Vagelos HR, Yee YG, Benedict CR, et al. Neurohormonal and clinical responses to high- vs. low-dose enalapril therapy in chronic heart failure. JACC 2002;39:70–8.
[38] Kramer BL, Massie BM, Topic N. Controlled trial of captopril in chronic heart failure: a rest and hemodynamic study. Circulation 1983;67:807–16.
[39] Nicholls MG, Ikram H, Espiner EA, Webster WI, Fitzpatrick MA. Enalapril in heart failure. Br J Clin Pharmacol 1984;18: 163S–7S.
[40] Jennings G, Kiat H, Nilson L, Kelly MJ, et al. Enalapril for severe congestive heart failure. Med J Aust 1984;141:723–6.
[41] Joy M, Hubner PJ, Thomas RD, Cummin P, et al. Long-term use of enalapril in the treatment of patients with congestive heart failure. Int J Cardiol 1987;16:137–44.
[42] Riegger GAJ. Effects of quianpril on exercise tolerance in patients with mild to moderate heart failure. Eur Heart J 1991;12:705–11.
[43] Magnani B. Converting enzyme inhibition and heart failure. Am J Med 1988;84(Suppl 3A):87–91.
[44] The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. J Am Med Assoc 1988;259: 539–44.
[45] Barabino A, Galbariggi G, Pizzorni C, Lotti G. Comparative effects of long-term therapy with captopril and ibopamine in chronic congestive heart failure in old patients. Cardiology 1991;78:234–56.
[46] Meyer TE, Casadel B, Coats AJS, Davey PP, et al. Angiotensin converting enzyme inhibition and physical training in heart failure. J Int Med 1991;230:407–13.
[47] Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. N Engl J Med 1988;319:80–6.
[48] O'neill CJA, Charlett A, Dobbs RJ, Deshmukh AA, et al. Effect of captopril on functional, physiological and biochemical outcome in aged heart failure patients. Br J Clin Pharmacol 1992;33:167–78.
[49] Northridge DB, Rose E, Raftery ED, Lahiri A, et al. A multicentre, double-blind, placebo-controlled trial of quinapril in mild, chronic heart failure. Eur Heart J 1993;14:403–9.
[50] Corder CN, Rubler S, Deere LF, Puls A, et al. Effect of cilazapril on exercise tolerance in congestive heart failure. Pharmacology 1993; 46:148–54.
[51] Tanabe K, Suzuki N, Osada N, Yamamoto A, et al. Effects of cilazapril on exercise tolerance in the chronic phase of acute myocardial infarction. Jpn Circ J 1996;60:831–40.
[52] Young JB, Gheorghiade M, Uretsky BF, Patterson JB, Adams FK. Superiority of 'triple' drug therapy in heart failure: insights from PROVED and RADIANCE trials. JACC 1998; 32:686–92.
[53] Northridge DB, Currie PF, Newby DE, McMurray JJV, et al. Placebo-controlled comparison of candoxatral, an orally active neutral endopeptidase inhibitor, and captopril in patients with chronic heart failure. Eur J Heart Failure 1999;1:67–72.
[54] Pacher R, Stanek B, Globits S, Berger R, Hulsmann M, et al. Effects of different enalapril dosages on clinical, haemodynamic and neurohormonal response of patients with severe congestive heart failure. Eur Heart J 1996;17:1223–32.
[55] Cooke GA, Williams SG, Marshall P, Al-Timman JK, et al. A mechanistic investigation of ACE inhibitor dose effects on aerobic exercise capacity in heart failure patients. Eur Heart J 2002;23:1360–8.
[56] Hartley LH, Flaker G, Basta L, Menapace F, et al. Physical working capacity after acute myocardial infarction in patients with low ejection fraction and effect of captopril. Am J Cardiol 1995;76: 857–60.
[57] Pflugfelder PW, Baird MG, Tonkon MJ, DiBianco R, Pitt B. Clinical consequences of angiotensin-converting enzyme inhibitor withdrawal in chronic heart failure: a double blind, placebo controlled study of quinapril. J Am Coll Cardiol 1993;22:1557–63.
[58] Kiowski W, Sutsch G, Dossegger L. Clinical benefit of angiotensin-converting enzyme inhibitor in chronic heart failure. J Cardiovasc Pharmacol 1996;27(Suppl 2):S19–24.
[59] Lubsen J, Chadha DR, Yotof YT, Swedberg K. Meta-analysis of morbidity and mortality in five exercise capacity trials evaluating

ramipril in chronic congestive heart failure. Am J Cardiol 1996;77: 1191–6.
[60] Andrew O, Mike C, editors. Cochrane reviewers' handbook 4.1.5. in: The Cochrane library issue 2, 2002. Oxford, UK. Updated software, updated quarterly.
[61] Abdulla J, Kober L, Torp-Pedersen C. Effect of angiotensin-converting inhibitor trandolapril on functional status and furosemide consumption in patients with reduced left ventricular function after myocardial infarction. J Am Coll Cariol 2003; 41(Suppl A):206A.
[62] Working group on cardiac rehabilitation and exercise physiology and working group on heart failure of the European Society of Cardiology. Recommendations for exercise testing in chronic heart failure patients, Eur Heart J 2001; 22:37–45.