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Effect of angiotensin-converting enzyme inhibition on functional class in patients with left ventricular systolic dysfunction—a meta-analysis

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Abstract

Background: The effect of angiotensin converting enzyme (ACE) inhibitors on symptoms in patients with left ventricular systolic dysfunction (LVSD) is controversial.
Aims: To perform a meta-analysis of studies evaluating effect of ACE inhibitors on New York Heart Association (NYHA) class in patients with LVSD.
Methods: Individual data from 10389 patients in NYHA classes I–IV from four large long-term studies (2–4-year follow-up) and summary data from 2302 patients in NYHA classes II–IV from 16 short-term studies (3 months follow-up) were meta-analysed to assess changes in NYHA class.
Results: The large long-term studies showed a significant improvement in the worst NYHA classes (classes II–IV compared to class I) in the ACE inhibitor arm versus placebo, odds ratio (OR)=0.875 (0.811–0.943) $p=0.0005$. This effect was only present in studies which included patients with chronic heart failure and was particularly pronounced on deterioration to the worst NYHA class IV, OR=0.66 (0.52–0.84) $p=0.001$. There was no effect in the studies which included patients after myocardial infarction. The short-term chronic heart failure studies showed a significant improvement in NYHA class; OR for improvement of at least one NYHA class was 2.11 (1.48–2.98, 95% CI) $p<0.0001$.
Conclusion: ACE inhibition significantly improves symptomatic status measured as NYHA classification in patients with chronic heart failure.

Keywords: Angiotensin converting enzyme inhibitor; Congestive heart failure; Left ventricular dysfunction; Dyspnoea

1. Introduction

Symptom relief is an important clinical issue in congestive heart failure, particularly when the disease worsens and dyspnoea becomes the major complaint. Diuretics have been used effectively to alleviate symptoms, but it has been suggested that angiotensin-converting enzyme (ACE) inhibitors can improve New York Heart Association (NYHA) class and exercise capacity. This theory is based on studies that have shown that ACE inhibitors have improved NYHA class in addition to a marked reduction in mortality and hospitalization rate [1–3]. Nevertheless,

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the large mortality studies of ACE inhibitors have not addressed this important issue in detail [4–7]. The Studies Of Left Ventricular Dysfunction (SOLVD)-Treatment Trial showed that enalapril improved a dyspnoea scale (0–5) over the first year but this effect was not maintained [8]. Recently, analyses from the TRAndolapril in Cardiac Evaluation (TRACE) study demonstrated that trandolapril did not improve NYHA class significantly in myocardial infarction patients with left ventricular systolic dysfunction (LVSD) [9]. The results are conflicting and need further clarification. ACE inhibitors are under-used [10], and further insight into symptomatic benefits could help future use. Therefore, we conducted a meta-analysis of the effect of ACE inhibitors on NYHA class.

2. Methods

2.1. Search strategy

Individual patient data from 3 large long-term ACE inhibitor studies of patients with LVSD-TRACE, SOLVD and Survival And Ventricular Enlargement Trial (SAVE) were available for the authors through the Joint Database of ACE Inhibitor Studies [4–7,11]. Methods used to identify relevant trials and combine individual patients data from these trials have been described previously [12]. Furthermore, we searched the medical literature through MEDLINE, EMBASE and Cochrane databases in English language for other trials using the following keywords: angiotensin-converting enzyme inhibitor, signs and symptoms, dyspnoea, exercise capacity and tolerance, congestive heart failure and choosing clinical trial and human without time limitation. Additionally, a manual search was conducted through abstracts, previous reviews and meta-analyses on ACE inhibitors in patients with LVSD.

2.2. Study selection

We selected published randomized controlled trials with a follow-up of at least 3 months, comparing the effect of ACE inhibitors versus placebo on NYHA class in patients with a clinically established diagnosis of heart failure or LVSD.

2.3. Data extraction

Six authors contributed to the extraction of individual patient data from the 3 large studies TRACE, SOLVD and SAVE. Two reviewers evaluated all other potentially eligible studies, data characteristics and performed data extraction.

2.4. Statistics

Odds ratio was chosen as a measure for treatment effect on NYHA class and mortality in all analyses. Individual patient data from the large long-term and summary data from the short-term studies were analyzed independently. A proportional odds model for ordinary response was fit treating the large studies as fixed effects model. The summary data of the long-term studies and the study by Kleber were combined only in a single analysis comparing patients in NYHA class IV. The summary data on NYHA class from the 16 short-term studies were pooled as numbers of patients improved and not-improved (unchanged and worsened) in each treatment arm at the end of the studies. This analysis provided the odds ratio for improvement or no-improvement in the treatment versus the placebo arm. The mortality analyses were performed comparing number of deaths in the ACE inhibitor arm with number of survivors versus the same in the placebo arm. The pooled odds ratios of these studies were meta-analyzed using Peto-Yusuf method for fixed effects, DerSimonian-Laird method for random effects and Chi Squared test was used for between study heterogeneity. In one study [13] each arm of the two different ACE inhibitors (cilazepril and captopril) was analyzed independently for change in NYHA class. All p-values < 0.05 with 95% confidence interval were considered significant. The meta-analyses, plots and meta-regression analysis were done using STATA version 8 (Stata Corporation, Lakeway Drive, College Station, Texas, USA) and Statistical Analysis System version 8 (SAS Institute, Cary 118 Inc., North Carolina, USA).

3. Results

In addition to the 3 large studies TRACE, SOLVD and SAVE [4–6,11], the electronic and manual search revealed 93 randomized controlled trials that were potentially eligible. The full text versions of all of these studies were retrieved for manual evaluation. Of the total, only 26 published studies evaluated changes in NYHA class [1,2,7,13–35]. Of these, two large studies were excluded because the authors could not provide the required data [7,20] and 7 other studies were excluded because of either insufficient data or data not compatible with the other eligible studies [14–19,21]. These 9 excluded studies comprised 2860 patients, constituting 17.5% of the total population from the 26 studies. Therefore, data from 3 large long-term studies (the SOLVD study was in two parts) from the Joint Database of ACE Inhibitor Studies [4–6] and a study by Kleber [2] were eligible for the long-term analysis (2–4 years follow-up). While another 16 studies [1,13,22–35] were eligible for the short-term (3 month) analysis. Eleven of these 16 studies [13,26–35] were multi-centre studies which primarily investigated the effect of ACE inhibition on exercise tolerance after 3 months follow-up, four studies were single-centre small sample studies also with 3-months follow-up [22–25] and finally the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS-I) was a survival study with 12 months follow-up

[1]. These 16 studies reported the summary of changes in NYHA class as the total number of patients who were improved, unchanged or worsened. Improvement or worsening was defined as a change by at least one NYHA class in either direction. Data on change in each NYHA class were unavailable in these studies. Meanwhile the large long-term studies supplied individual patient data on worst NYHA class observed during the follow-up period, which enabled us to compare the effect of the treatment in each NYHA class IV–II. The study by Kleber et al. [2] supplied summary data only on deterioration from NYHA classes I–III to IV.

All the included 20 studies were randomized, controlled and double-blind, and reported the number of deaths in each arm. NYHA class at baseline and follow-up of the patients included in these studies are shown in Tables 1 and 2. To show mortality in the tables together with NYHA class, death is shown as NYHA class V. The short-term studies and the CONSENSUS-I study had almost an exclusively symptomatic population of patients with chronic heart failure in NYHA classes II–IV at baseline. In contrast the large long-term studies had a considerable number of asymptomatic patients in NYHA class I. The TRACE and SAVE studies included patients after acute myocardial infarction (AMI) with LVSD.

3.1. The effect on the worst NYHA class

In the large long-term studies, the treatment with ACE inhibition produced odds ratio = 0.875 (0.811–0.943) $p = 0.0005$ corresponding to 12.5% reduction of having a NYHA class IV versus classes I–III, classes III–IV versus classes I–II, and classes II–IV versus class I. Fixed and random effects models showed the same results. The studies were homogenous, $p = 0.248$ for heterogeneity. By adding the study by Kleber only to the analysis of NYHA class IV versus I–III the odds ratio was 0.70 (0.56–0.87) $p = 0.001$ and the studies were still homogenous, $p = 0.326$ for heterogeneity (Fig. 1). Previously, the death and readmission in these studies was

Table 1
Baseline and worst New York Heart Association (NYHA) class at follow-up in 10389 patients included in the long-term studies. Mortality was considered as NYHA class V

Study, average follow-up period and mean baseline LVEF	NYHA class	Number (%) of patients at baseline		Number (%) of patients at follow-up	
		ACEI	Placebo	ACEI	Placebo
TRACE* [6] 36 months LVEF = 30%	I	372/860 (43.2)	340/851 (39.9)	132/713 (18.5)	105/699 (15.0)
	II	348/860 (40.4)	364/851 (42.7)	415/713 (58.2)	404/699 (57.8)
	III	92/860 (10.7)	89/851 (10.4)	145/713 (20.3)	169/699 (24.1)
	IV	48/860 (5.6)	58/851 (6.8)	21/713 (2.9)	21/699 (3.0)
	V	NA	NA	304/860 (35)	369/851 (43)
SOLVD† [11] Prevention Trial 37 months LVEF = 28%	I	1399/2111 (66.3)	1420/2117 (67.1)	773/2103 (36.7)	769/2106 (36.5)
	II	712/2111 (33.4)	697/2117 (32.7)	1127/2103 (53.5)	1050/2106 (49.8)
	III	NA	NA	189/2103 (8.9)	262/2106 (12.4)
	IV	NA	NA	14/2103 (0.6)	25/2106 (1.1)
	V	NA	NA	313/2111 (14.8)	334/2117 (15.7)
SOLVD† [4] Treatment Trial 41 months LVEF = 25%	I	146/1285 (11.4)	135/1284 (10.5)	60/1271 (4.7)	38/1267 (3.0)
	II	729/1285 (56.8)	726/1284 (56.6)	567/1271 (44.6)	526/1267 (41.5)
	III	386/1285 (30.1)	394/1284 (30.7)	542/1271 (42.6)	569/1267 (44.9)
	IV	19/1285 (1.5)	24/1284 (1.9)	102/1271 (8.0)	134/1267 (10.5)
	V	NA	NA	452/1285 (35.2)	510/1284 (39.7)
SAVE‡ [5] 42 months LVEF = 31%	I	ND	ND	740/1115 (66.3)	731/1115 (65.5)
	II	ND	ND	299/1115 (26.8)	317/1115 (28.4)
	III	ND	ND	75/1115 (6.7)	65/1115 (5.8)
	IV	ND	ND	1/1115 (0.09)	2/1115 (0.18)
	V	NA	NA	228/1115 (20)	503/1115 (25)
Kleber [2] 2.7 years (median) LVEF = 35%	I	23/83 (27)	22/87 (25)	NA	NA
	II	43/83 (52)	42/87 (48)	NA	NA
	III	18/83 (21)	23/87 (26)	NA	NA
	IV	NA	NA	9/83 (11)	23/87 (26)
	V	NA	NA	22/83 (26.5)	22/87 (25.2)
Total	I	2680/5454	2648/5454	1705/5202 (32.7)	1643/5187 (31.6)
	II	2131/5454	2146/5454	2408/5202 (46.2)	2297/5187 (44.2)
	III	571/5454	571/5454	951/5202 (18.2)	1065/5187 (20.5)
	IV	68/5454	84/5454	147/5202 (2.6)	205/5187 (3.5)
	V	NA	NA	1319/5454 (24)	1738/5454 (31.8)

ACEI = angiotensin converting enzyme inhibitor, NA = not available, ND = not done, LVEF = left ventricular ejection fraction. *TRACE = TRAndolapril Cardiac Evaluation study, †SOLVD = The Studies on Left Ventricular Dysfunction, ‡SAVE = Survival And Ventricular Enlargement Trial. SAVE was an early post-myocardial infarction study in asymptomatic patients therefore the NYHA class was recorded only at follow-up.

Table 2
New York Heart Association (NYHA) class of 2302 patients with chronic heart failure at baseline and end of the short-term studies (changed at least one NYHA class)

Study or author name/Publication year	Baseline population ACEI/placebo	Number of patients improved ACEI/placebo	Number of patients not improved ACEI/placebo
The multi-centre studies			
Captopril Multi-centre Research Group, 1983 [26]	50/42	30/10	17/18
Cooperative North Scandinavian Enalapril Survival Study-I, 1987 [1]	127/126	16/2	39/38
Captopril-Digoxin Multi-centre Research Group, 1988 [27]	104/100	41/21	59/77
Rieger, 1991 [28]	150/47	68/14	82/33
Colfer, 1992 [29]	114/58	30/7	68/38
Lechat, 1993 [30]	61/64	31/16	25/41
Dosseger, 1993 [31]	72/35	37/11	33/22
Gundersen, 1994 [32]	115/108	28/33	76/58
Brown, 1995 [33]	116/125	27/16	87/103
Cilazapril-Captopril Multi-centre Group, 1995 [13] (cilazapril/captopril/placebo)	221/108/114	66/31/28	125/57/59
Erhardt, 1996 [34]	155/153	52/38	75/80
Hampton, 1998 [35]	148/144	28/27	96/105
NYHA class in the multi-centre studies			
I	8/2651 (0.3%)	NA	NA
II	1596/2651 (60%)	NA	NA
III	780/2651 (29.7%)	NA	NA
IV	267/2651 (10%)	NA	NA
Total (ACEI/Placebo)	1532 (58%)/1119 (42%)	485 (37%)/223 (24%)	838 (63%)/672 (76%)
NYHA V (ACEI vs. placebo)	72/1395 (5%) vs. 100/995 (10%)		
The small sample studies (NYHA class unavailable)			
Sharpe, 1984 [22]	18/18	12/2	2/12
McGrath, 1985 [25]	13/12	10/2	3/10
Chrysant, 1985 [23]	7/7	3/0	4/7
Drexler, 1989 [24]	9/8	7/0	2/8
Total of the small sample studies (ACEI/Placebo)	47 (51%)/45 (49%)	32 (74%)/4 (10%)	11 (26%)/37 (90%)
NYHA V (ACEI vs. placebo)	1/43 (2.5%) vs. 4/41 (9.5)		

ACEI=angiotensin converting enzyme inhibitor, NA=not available.

estimated as odds ratio of 0.74 (0.69–0.80) $p<0.0001$ [12]. Although these studies were statistically homogenous, further analyses according to the setting of the heart failure were performed by sorting the studies into chronic heart failure and post-AMI categories. These analyses showed a significant effect imposed by the chronic heart failure studies OR=0.66 (0.52–0.84) $p=0.001$, but not by the post-MI studies OR=0.94 (0.52–1.7) $p=0.83$ (Fig. 1). A meta-regression analysis that was performed particularly to explore whether the baseline mean ejection fraction in all long-term studies had any influence on the treatment effect on deterioration to NYHA class IV, showed no significant effect, $p=0.067$.

Due to significant heterogeneity ($p=0.0001$) the short-term studies were analysed by random effects model. The odds ratio for improvement of at least one NYHA class was 2.11 (1.48–2.98, 95% CI) in the ACE inhibitor versus placebo arm, $p<0.0001$ (Fig. 2)—this corresponded to odds ratio of 0.48 (0.34–0.67) for deterioration or no-improvement in treatment versus the placebo arm. The fixed effects model showed OR of 1.76 (1.47–2.10, 95% CI). The heterogeneity in these studies was partly due to the small sample size; by excluding these studies the p-value for heterogeneity was reduced to 0.011.

3.2. The effect on mortality (NYHA V)

Mortality analyses only on the studies including patients with chronic heart failure showed significant reduction in all cause mortality combining all studies together and separately according to each term (Fig. 3). Combining all 20 studies including the TRACE and SAVE studies also showed a significant reduction in all cause mortality OR=0.065 (0.47–0.89), $p=0.008$.

4. Discussion

This review and meta-analysis of the studies assessing the effect of ACE-inhibition on NYHA class in patients with

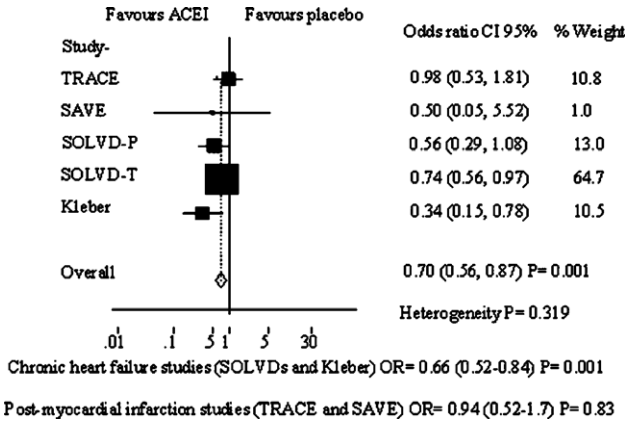

Fig. 1. Forest plot of meta-analysis of the 4 long-term studies showed significant beneficial effect of angiotensin converting enzyme inhibitors (ACEI) on deterioration from New York Heart Association classes I–III to the worst class IV in patients with chronic heart failure. TRACE=TRAndolapril Cardiac Evaluation, SOLVD=The Studies on Left Ventricular Dysfunction, SAVE=Survival And Ventricular Enlargement.

LVSD shows that patients with LVSD benefit from ACE inhibition but this significant benefit was evident only in patients with chronic heart failure and not in patients with LVSD after AMI. The effect was similarly significant both in the short- and long-term studies, indicating that the effect is maintained over a long time. This may explain why some heart failure patients improve their NYHA class after treatment with ACE inhibition while others do not. This difference in effect is difficult to interpret, but it may be attributed to the clinical setting of the heart failure during which the patient initiates therapy. However, it is still difficult to exclude a possible beneficial effect in patients with LVSD after AMI, because the initial treatment of this category of patients usually takes place during hospital admission, where strict regulation of concomitant medication particularly diuretics continues until discharge and

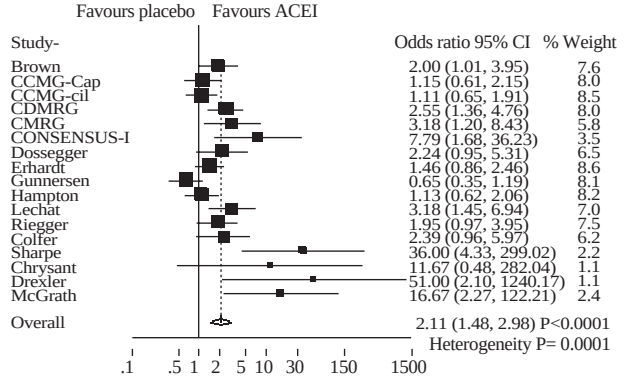

Fig. 2. Forest plot of meta-analysis of the 12 multi-centre and 4 small sample studies (the last four) after 3 months follow-up showed significant improving effect of angiotensin converting enzyme inhibition (ACEI) on New York Heart Association class in patients with chronic heart failure. CCMG=Cilazapril-Captopril Multi-centre Group, Cap=captopril, Cil=cilazapril, CMRG=Captopril Multi-centre Research Group, Captopril-Digoxin Multi-centre Research Group, CONSENSUS-I=Cooperative North Scandinavian Enalapril Survival Study-I.

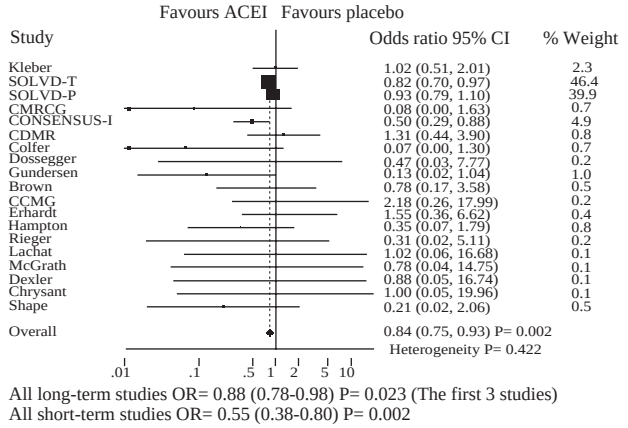

Fig. 3. Meta-analysis of mortality of the chronic heart failure studies that also evaluated New York Heart Association class. There was significant reduction in all cause mortality.

during the follow-up period. Such treatment–particularly excessive diuretic use in placebo arm–might mask the symptomatic effect of ACE inhibition.

There are a number of important potential biases in the reported analyses. Mortality and dropouts during short-term studies could have affected the results, because the analysis based on changes in NYHA class was only reported in patients who completed the studies. Another source of bias could be the lack of potential for deterioration in patients with NYHA class IV or for improvement in NYHA class I. Accordingly, the major changes might have occurred in patients with NYHA classes II–III in either direction. However, the number of patients in NYHA classes I and IV comprised only 10% of the whole population. An additional reason why the observed differences may be an underestimate of the true benefit, is that when patients deteriorate other drugs that affect symptoms, in particular diuretics and digoxin may be added.

Due to the way the studies were reported, not all studies could be included in the meta-analysis. The magnitude of the beneficial effect could thus differ from that reported, but the substantial number of studies and patients available provide a convincing case for the beneficial effect of ACE inhibition on symptoms to be real. In the data extracted from the long-term studies, fewer data were lost by comparing worst reported NYHA class observed. This procedure generates the possible bias of the reported NYHA being a reflection of an acute worsening of the condition rather than a reflection of the general clinical condition. The fact that NYHA class was obtained during regular visits reduced this bias.

Dissimilar use of diuretics could confound the results of studies evaluating NYHA class, since diuretics alleviate dyspnoea and therefore improve patients' NYHA class. Several of the reviewed studies reported increased use of diuretics in the placebo arm or decreased use in the ACE inhibitor arm during the treatment period [1,5,13,27,29,32–34]. The TRACE study analyzed the mean difference of furosemide dose between the placebo and trandolapril arms throughout 4 years of follow-up and reported an average

reduction of 12 mg/day in the trandolapril group as well as similar improvement of NYHA class in both treatment arms [9]. It is possible that use of diuretics in the placebo arm contributed to minimize the effect of ACE inhibition on NYHA class. Accordingly, the improvement in NYHA class in the ACE inhibitor arm could not be attributed to concomitant diuretic use; conversely this improvement might have been larger if diuretic use had been similar in both treatment arms.

This beneficial effect of ACE inhibition on NYHA class in patients with chronic heart failure and LVSD is concordant with the documented beneficial effect on exercise tolerance [36]. This consistency in the beneficial effect of ACE inhibition on these different end-points indicates that ACE inhibition improves not only survival but the functional status of patients with chronic heart failure and LVSD as well.

In conclusion, this systematic meta-analysis of long-and short-term studies demonstrated that NYHA class or worst reported NYHA class was improved by ACE inhibitor therapy in patients with chronic heart failure and LVSD. This benefit adds to the well known benefit of reducing mortality and morbidity [12] (Fig. 3).

Acknowledgements

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