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Review

A systematic review: Effect of angiotensin converting enzyme inhibition on left ventricular volumes and ejection fraction in patients with a myocardial infarction and in patients with left ventricular dysfunction

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Abstract

Background and aim: To summarize and quantify results of echocardiographic studies examining the effect of angiotensin converting enzyme (ACE) inhibition on left ventricular remodelling in patients with acute myocardial infarction (MI) and in patients with left ventricular systolic dysfunction (LVSD).
Methods: Systematic review of the literature and meta-analysis of eligible studies providing data on end-diastolic and end-systolic volumes and left ventricular ejection fraction (LVEF) were performed.
Results: Data from 16 eligible studies were meta-analysed. The results of studies including patients with MI and preserved LVEF (>45%) showed no significant benefit of ACE inhibition. Results of studies/subgroups with mean LVEF $\leq$45% demonstrated significant differences in diastolic and systolic volumes of 3.0 (0.1, 6.0) ml and 2.25 (0.04, 4.4) ml in short-term (4–14 weeks) follow-up in favour of ACE inhibitor, $p=0.041$ and $p=0.046$ respectively. In the long-term (6–12 months) follow-up, the differences in diastolic and systolic volumes were 4.2 (0.98, 7.4) ml and 3.3 (0.9, 5.8) ml in favour of ACE inhibitor, $p=0.01$ and $p=0.007$ respectively. LVEF improved in both short and long-term follow-up, $p=0.034$ and $p=0.021$, respectively.
Conclusion: Chronic use of ACE inhibition has a small but sustained and beneficial effect on remodelling in patients with myocardial infarction and patients with chronic left ventricular dysfunction.

Keywords: Angiotensin converting enzyme inhibitor; Remodelling; Diastolic and systolic volume; Ejection fraction

1. Introduction

Pivotal studies in rats generated the hypothesis that continued left ventricular dilatation following a myocardial infarction (MI)-ventricular remodelling — could be attenuated with an angiotensin converting enzyme (ACE) inhibitor [1,2]. Following the demonstration of this beneficial effect of captopril on remodelling in two small human studies [3,4], it was generally perceived that reduced remodelling could be the main effect of ACE inhibition. Subsequently, echocardiographic studies in patients with acute MI and left ventricular systolic dysfunction (LVSD) showed a favourable effect of ACE inhibition on remodelling and survival [5,6]. The results of the echocardiographic sub-study of Left Ventricular Dysfunction (SOLVD) trials in patients with established LVSD showed also a beneficial

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effect of ACE inhibition after 3–12 months in patients with chronic LVSD [7]. Later, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-3 (GISSI-3) trial showed an evident attenuating effect of early lisinopril administration on left ventricular volumes in 1800 patients with MI [8]. Patients with relatively preserved left ventricular ejection fraction (LVEF) failed to demonstrate a significant effect of ACE inhibition [8,9]. In general, the results of trials in patients with LVSD revealed a significant effect of ACE inhibition on cardiac remodelling, but in many studies this effect was modest and could not fully explain the benefit of ACE inhibition on the clinical outcomes [10]. Given the mixed findings, a comprehensive systematic review of these subjects is important to clarify the overall results of these studies. Therefore, we conducted this systematic review and meta-analysis to summarize the results, to quantify the magnitude of changes in ventricular volumes and to evaluate to what extent ACE inhibition prevents myocardial remodelling in patients with MI and patients with LVSD.

2. Methods

2.1. Search strategy

We searched the medical literature through MEDLINE, EMBASE and Cochrane electronic databases for all clinical trials using the following keywords: angiotensin converting enzyme inhibitor, congestive heart failure, left ventricle, remodelling, diastolic and systolic volume, ejection fraction, clinical trial, and human, without time limitation. Additionally, a manual search was conducted through previous reviews, meta-analyses and abstracts on ACE inhibitors and remodelling. All references were screened for eligible studies. Experts in this field were consulted.

2.2. Study criteria and selection

Randomised controlled trials evaluating the effect of ACE inhibition on left ventricular remodelling (end-diastolic and end-systolic volumes, LVEF) measured by 2-dimensional echocardiographic methods in patients with MI or in patients with LVSD were considered eligible for inclusion in the meta-analysis. We decided not to include studies that used other imaging techniques to avoid methodological heterogeneity. Short-term and long-term treatments were defined as treatment lasting at least 1–4 months and 6–12 months, respectively. Thus, studies with a follow-up period of less than 4 weeks were not included. LVSD was defined as LVEF $\leq$45%.

2.3. Data extraction

Two reviewers evaluated all potentially eligible studies, data characteristics and performed data extraction from the published papers. Additional data extraction in two studies were provided by their authors [8,11]. Results of studies reporting ventricular volumes in indexed data were converted to non-indexed data using the calculated mean body surface area (BSA) = 1.9 ± 0.18 M^2 [9,12–16].

2.4. Statistics

The measured mean non-indexed diastolic or systolic volumes and LVEF at study-end of each term (short and long) were compared between the ACE inhibitor and placebo/control arms. This meta-analytic comparison provided the weighted mean difference (95% confidence interval) of changes observed in ventricular volumes or LVEF. The analyses were performed using the summary data of numbers of patients who completed trials. Heterogeneity between studies was analysed using Chi squared test. The analyses were fit in models treating trials as fixed effects model; however, all analyses were also repeated using random effects model. All standard errors of means were recalculated to their standard deviations [9,13,15–20]. Unreported standard deviation at study-end were substituted by their baseline standard deviations [17,19–22]. All p-values <0.1 were considered statistically significant. The meta-analyses were performed using the statistical software package STATA-8 (Stata Corporation, Lakeway Drive, College Station, Texas, USA).

3. Results

3.1. Results of the search

After search and sorting by title, abstracts or full texts, 97 randomised controlled studies were retrieved for further evaluation. A review of the full text of these studies revealed that only 27 studies met the criteria for evaluating remodelling and provided data on changes in ventricular volumes and LVEF. Eight studies which used other imaging techniques than echocardiography were excluded. Two studies were excluded because the ventricular dimensions were measured as area (cm^2) and not volume (ml) and for these studies the efforts made to obtain the converted data in volume failed [23,24]. One study which examined patients with preserved LVEF and without MI was also excluded as the study was not eligible to be combined with either the MI studies or with the non-MI studies with LVSD [25]. Eventually, a total of 16 potentially eligible studies were identified for the meta-analysis (Table 1).

3.2. Characteristics of the studies and populations

All studies were randomised controlled and the majority were double-blind [7,9,13–16,19–22]. Controls received placebo except in two studies [8,26]. The intention-to-treat principle was used in analysis of the majority of the

Table 1
Characteristics of the included studies and subgroups

MI Studies LVEF>45%	Type of ACEI	Follow-up period
CAPTIN [9]	Captopril	3 months
CATS [15]	Captopril	3–12 months
EDEN [12]	Enalapril	14–26 weeks
FAMIS [16]	Fosinopril	3 months
GISSI-3 (subgroup) [8]	Lisinopril	6 weeks–6 months
Rasmussen [22]	Ramipril	6 months
MI studies LVEF ≤45%		
Baur [30]	Enalapril	12 months
CONSENSUS-II (subgroup) [19]	Enalapril	1–6 months
GISSI-3 (subgroup) [8]	Lisinopril	6 weeks–6 months
Oldroyd [17,31]*	Captopril	2–12 months
Sharpe-1 [20]	Captopril	3–12 months
Sharpe-2 [21]	Captopril	3 months
Shen [26]	Captopril	12 months
Sogaard [13]	Captopril	3–6 months
Non-MI studies LVEF ≤45%		
Keren [18]	Captopril	12 months
Kjoller [14]	Ramipril	3–12 months
SOLVD**[7]	Enalapril	4–12 months

ACEI = angiotensin converting enzyme inhibitor, LVEF=left ventricular ejection fraction, MI = myocardial infarction.
Abbreviations of the studies: CAPTIN = CAPtopril plus Tissue Plasminogen activator following acute myocardial INfarction, CATS = Captopril And Thrombolysis Study, CONSENSUS-II = COoperative New Scandinavian ENalpril SUrvival Study, EDEN = Study of enalapril in ventricular dysfunction after myocardial infarction, FAMIS = Fosinopril in Acute Myocardial Infarction Study, GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico, SOLVD = Study Of Left Ventricular Dilatation Trial.
* The data in this study were published in two articles [17,31].
** SOLVD study had a majority of patients with ischemic heart disease in background.

included studies, but this was not clearly indicated in a number of small studies [13,18,20–22]. Characteristics of the included studies are shown in Table 1. The total number of patients included in the analyses was 8490; 4277 patients were treated with an ACE inhibitor and 4213 patients were treated with placebo. Six different ACE inhibitors were used. The mean age of the participants was 60.2 years, 83% were male and mean baseline LVEF was 43.3%. Three studies included patients with chronic heart failure and/or LVSD [7,14,18] the remaining 13 studies included patients after an acute MI. In the MI studies echocardiography was performed after 1–10 days of hospitalisation except for the GISSI-3 study [8] where the first echocardiography was performed before discharge (mean hospital stay was 14 days).

The meta-analysed data are shown in Table 2.

3.3. Studies/subgroups of patients with LVEF> 45%

In the analyses of ventricular volumes, an overall negative weighted mean difference indicating a reduction in volumes in the ACE inhibitor compared to the placebo arm was defined as improvement. In the analyses of LVEF, an overall positive result indicating an increase in LVEF in the ACE inhibitor compared to the placebo arm was defined as improvement.

Meta-analyses of 5 studies [9,12,15,16,22] and a subgroup of the GISSI-3 study with preserved LVEF (2887 received ACE inhibitor versus 2804 received placebo or were controls) [8] showed a slight improvement in diastolic volume in the short-term but not in the long-term. There was no significant improvement in systolic volume. The short-term analysis showed an improvement of −1.64 (−3.21, −0.08) ml in diastolic and −0.53 (−1.47, 0.40) ml in systolic volume, p-values were 0.040 and 0.269, respectively, heterogeneity between studies were not significant $p=0.638$ and $p=0.523$, respectively. The long-term analysis showed an improvement of −1.24 (−2.93, 0.44) ml in diastolic and −0.23 (−1.28, 0.80) ml in systolic volume, p-values were 0.149 and 0.657, respectively and heterogeneity between studies was not statistically significant, $p=0.547$ and 0.293, respectively.

3.4. Studies/subgroups of patients with LVEF ≤45%

These analyses included 2799 patients, of these 1390 received an ACE inhibitor and 1409 received placebo or were controls. There was significant heterogeneity between the studies. In contrast to studies of preserved LVEF, combining studies or subgroups of patients with low LVEF (≤45%) demonstrated significant improvement in ventricular volumes and LVEF.

Combining 8 studies showed a significant reduction in left ventricular diastolic volume in the short-term follow-up (4–14 weeks), the fixed model showed a significant improvement of −3.08 (−6.03, −0.13) ml $p=0.041$, heterogeneity $p=0.097$. The random model showed a larger improvement of −6.71 (−12.04, −1.37) ml $p=0.014$.

The improvement in systolic volume was −2.25 (−4.46, −0.04) ml $p=0.046$, heterogeneity $p=0.030$ by fixed effects model and −7.21 (−12.31, −2.1) ml $p=0.006$ by random effects model.

In the long-term analyses there was also significant improvement in ventricular volumes measured in the ACE inhibitor compared to the placebo arm, Figs. 1 and 2.

3.5. Low LEVF with and without MI

Studies/subgroups characterised by low LVEF (≤45%) were sorted further according to the clinical characteristics of patients into those with MI and those without MI (non-MI). In the short-term analysis, combining 5 MI studies showed an improvement of −2.11 (−5.30, 1.07) ml in diastolic volume with $p=0.194$ and heterogeneity $p=0.090$, while the 3 non-MI studies showed a difference of −8.75 (−16.47, −1.02) ml with $p=0.026$ and heterogeneity $p=0.685$. The improvement in systolic volume in the 5 MI studies was −2.1 (−4.42, 0.09) ml $p=0.060$ heterogeneity $p=0.017$ and in non-MI studies was −6.25 (−13.46,

Table 2
The meta-analysed echocardiographic measurements

Study/author and number of patients ACEI/Placebo or control	Ventricular measurements	Short-term (4–14 weeks)		Long-term (6–12 months)	
		ACEI	Placebo or control	ACEI	Placebo or control
Sharpe-1 [20] 30/30	EDV ml/m^2	79.1±NA	79.7±NA	78.2±NA	82±NA
	ESV ml/m^2	47.8±NA	52.8±NA	45±NA	53±NA
	LVEF %	41.0±NA	34.5±NA	43.3±NA	35.8±NA
Sharpe-2 [21] 50/50	EDV ml/m^2	74.8±NA	77.2±NA	NA	NA
	ESV ml/m^2	41.8±NA	46.0±NA	NA	NA
	LVEF %	45.0±NA	41.2±NA	NA	NA
Oldroyd [17,31] 31/36	EDV ml/m^2	76.3±17.8	82.8±15	Δ8.4±NA	Δ19.0±NA
	ESV ml/m^2	46.4±17.2	53.7±16.2	Δ5.4±NA	Δ14.7±NA
	LVEF %	40.5±11	36±11	37.5±11	33±12
Sogaard [13] 29/29	EDV ml/m^2	74±16.7	80±22	73±17.7	83±24.2
	ESV ml/m^2	40±13.4	47±16.6	39±14	49±17.7
	LVEF %	43±5	41±6	48±6	40±5
CONSENSUS-II [19] 140/120 (All patients)	EDV ml/m^2	49.5±13	53.2±15.2	51.1±15.7	54.2±15.4
	ESV ml/m^2	26.5±12	29.6±13	27.2±12.7	29.8±13.2
	LVEF %	48±9	46±10	48.5±9	46.5±10
CONSENSUS-II-L 32/42 (subgroup)	EDV ml/m^2	Δ1.6±NA	Δ8.4±NA	Δ6.7±NA	Δ5.4±NA
	ESV ml/m^2	Δ−0.9±NA	Δ4.2±NA	Δ3.9±NA	Δ2.5±NA
	LVEF %	NA	NA	NA	NA
Keren [18] 25/16	EDV ml	NA	NA	269±100	282±136
	ESV ml	NA	NA	201±80	219±116
	LVEF %	NA	NA	NA	NA
SOLVD [7] 127/130	EDV ml	198±37	208±43	197±39	210±46
	ESV ml	147±36	155±43	145±38	156±42
	LVEF %	26±11	26±11	26±11	26±11
GISSI-3-P [8] 2268/2285 (subgroup)	EDV ml	89.2±28.4	90.8±28.8	90.5±29.6	91.5±30.2
	ESV ml	40.2±16.7	40.6±16.7	40.8±18.3	40.9±18.4
	LVEF %	55.4±9.1	55±7	55.5±9.3	55±8
GISSI-3-L 918/934 (subgroup)	EDV ml	105.4±40	105.3±39	107.5±45	108.4±41.5
	ESV ml	61.5±29	61.4±27	62±33.4	62.4±29.6
	LVEF %	42.5±9.7	42.5±9.4	44±10	43.5±10
CATS [15] 149/149	EDV ml/m^2	59.1±20.8	60.5±20	61.4±21	62.8±17.6
	ESV ml/m^2	25.3±15.2	26.9±15.2	30±16.1	29.5±14.8
	LVEF %	NA	NA	NA	NA
FAMIS [16] 107/111	EDV ml/m^2	61.7±15	63.3±18	NA	NA
	ESV ml/m^2	30.5±12	30.5±15	NA	NA
	LVEF %	52±10	53±12	NA	NA
CAPTIN [9] 132/130	EDV ml/m^2	56.8±22.8	55.2±16.6	NA	NA
	ESV ml/m^2	29±18	27.8±13	NA	NA
	LVEF %	NA	NA	NA	NA
Shen [26] 52/49	EDV ml	NA	NA	132±48	150±46
	ESV ml	NA	NA	71±35	93±32
	LVEF %	NA	NA	47±9	39±10
Baur [30] 29/27	EDV ml/m^2	NA	NA	61.9±22.7	59.4±17
	ESV ml/m^2	NA	NA	37±18.4	36.8±15.2
	LVEF %	NA	NA	41.8±9.9	39.2±11.6
Rasmussen [22] 18/20	EDV ml/m^2	NA	NA	50.1±NA	54±NA
	ESV ml/m^2	NA	NA	27.5±NA	27.9±NA
	LVEF %	NA	NA	46.8±NA	49.3±NA
EDEN [12] 213/109	EDV ml	113.8±45.5	120.9±41.4	111±49.5	119.5±43.1
	ESV ml	56.8±29	62.4±29.3	54.7±30.6	61.9±30.7
	LVEF %	51±11	49±11	51±10	49±10
Kjoller [14] 67/66	EDV ml/m^2	68.9±19	72.3±17.5	74.1±21.7	75.1±19.8
	ESV ml/m^2	44.5±16.1	46.6±16.2	47.4±19	48.1±17.7
	LVEF %	36.5±8.3	37.0±9.9	37.4±8.9	37.2±10.0

Ventricular volumes were measured either as indexed (ml/m^2) or non-indexed (ml) values or change from baseline (Δ). All values are presented as mean±standard deviation.

ACEI = angiotensin converting enzyme inhibitor, EDV = left ventricular end-diastolic volume, ESV = left ventricular end-systolic volume, LVEF = left ventricular ejection fraction, NA=not available.

Abbreviations of the studies: CAPTIN = CAPtopril plus Tissue plasminogen activator following acute myocardial INfarction, CATS = Captopril And Thrombolysis Study, CONSENSUS-II = COoperative New Scandinavian ENalapril SUrvival Study, CONSENSUS-II-L = subgroup with low EF, EDEN = Study of enalapril in ventricular Dysfunction after myocardial infarction, FAMIS = Fosinopril in Acute Myocardial Infarction Study, GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico, GISSI-3-P = subgroup with preserved LVEF, GISSI-3-L = subgroup with low LVEF, SOLVD = Studies Of Left Ventricular Dysfunction trial.

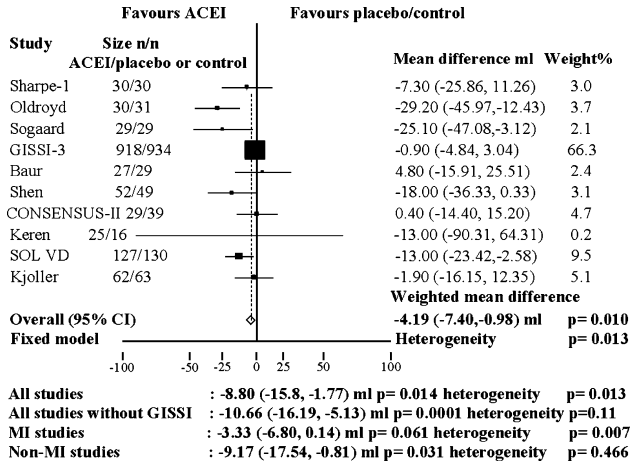

Fig. 1. Combining 10 studies with baseline left ventricular ejection fraction ≤45% showed a significant improvement in diastolic volume in the long-term follow-up (6–12 months). All analyses are in random effects model unless stated as fixed effects model.

0.94) ml $p=0.089$ heterogeneity $p=0.059$. Results of the long-term analysis are shown in Figs. 1 and 2.

Improvement in LVEF was present only in the MI studies with a value of 3.75 (0.68, 6.82) ml $p=0.016$ heterogeneity $p=0.0001$.

4. Discussion

This systematic review and meta-analysis included a large number of patients with MI and LVSD treated with ACE inhibitors versus placebo or control. The results in general were of significance in studies or subgroups examining patients characterised by LVEF ≤45%. In MI studies this finding reflected most likely a beneficial effect of ACE inhibition in patients who suffered larger infarcts. Although the studies that included patients with MI and relatively preserved LVEF showed no statistically significant improvement in ventricular volumes, a slight volume improvement in the ACE inhibitor arm was noticed.

As the studies included in this meta-analysis demonstrated a favourable effect on clinical outcomes, it may be reasonable to suggest a relationship between the favourable effect on remodelling and survival. Such a relationship has been suggested previously [5,23]. However, the overall magnitude of the attenuating effect on ventricular remodelling measured as volumes was not pronounced (4%) compared to the well-known effect on mortality (26% reduction in odds ratio) [27]. One reason for the small effect on volumes could be measurement inaccuracies. Another potential reason could be the lack of data with respect to strata of LVEF. The vast majority of the beneficial effect on volumes was observed in patients with a reduced LVEF and it is possible that this reflects an even greater effect in patients with severely reduced LVEF. Therefore, an underestimation of the true effect could also be attributed to the bias induced by mortality as more patients with severely reduced LVEF and ventricular dilation may have died without reaching the end-point.

The included studies showed some variation in the effect on ventricular volumes during the short- and long-term follow-up. Baseline characteristics, study design and some methodological differences between the studies may have contributed to such variations. It should also be emphasized that the short- and long-term measurements took place at different time-points with a variation between weeks to months respectively. Nevertheless, the overall results demonstrated that there was further improvement in the ventricular volumes and LVEF in the long-term studies compared with the short-term studies. The time factor possibly had a significant effect on the changes in volumes, but the difference in the number and characteristics of the meta-analysed studies in the short-versus the long-term makes such a conclusion uncertain.

It was interesting to note that the larger multi-centre studies [7,8] produced a minor volume improvement whereas the small mono-centre studies had a more robust effect with larger variation in the estimated effect size [13,18]. This was more evident in the largest and predominating GISSI-3 study that showed the least but still significant effect in the long-term. As this may indicate quality differences and ultimately heterogeneity between the studies, we also performed separate analyses excluding the GISSI-3 study.

This meta-analysis included a number of studies that were heterogeneous with regard to baseline patient characteristics and category. We combined studies including patients after a recent MI or patients without recent MI but with chronic heart failure. Patients in all these studies had an important common feature characterised by LVSD. This more liberal meta-analytic approach is useful to demonstrate the overall effect of ACE inhibitors in patients with LVSD in general. This approach has also been previously used to combine the large randomised controlled

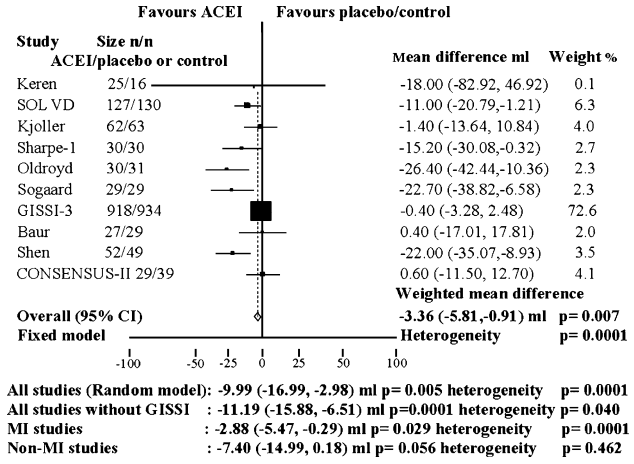

Fig. 2. Combining 10 studies with baseline left ventricular ejection fraction ≤45% showed a significant improvement in systolic volume in the long-term follow-up (6–12 months). All analyses are in random effects model unless stated as fixed effects model.

trials to estimate the effect of ACE inhibitors on the primary and even secondary end-points [27,28]. However, it is essential to demonstrate the effect of each study group in separate analyses. Another source of heterogeneity in the current meta-analysis was the variation in the effect size due to differences between the larger and smaller studies. In this context, an analysis of heterogeneity may not always be sensitive enough to detect a statistically significant heterogeneity and a decision based purely on a p-value is not to be recommended [29]. Therefore we attempted to choose a more conservative cut-off point of p-value of 0.1 in stead of 0.05, which means a p-value below 0.1 (for example 0.75) still indicates that significant heterogeneity may exist. This was evident in the analysis of the short-term studies with low LVEF where a p-value of 0.097 revealed a marked difference between the fixed and random effects models. On the other hand, although the estimated treatment effect (magnitude of the improvement in volumes) in a number of analyses were relatively large, the associated p-values were greater than the traditional value of 0.05. Examples are particularly: the results of the short-term analyses of the non-MI studies with an improvement of 6.25 ml in systolic volume with a p-value of 0.089, and again in the long-term analysis of the non-MI studies with an improvement of 7.4 ml in systolic volume but a p-value of 0.056. Conversely, it has been argued in the literature when combining studies in a random effects model, a more conservative approach should be the choice with a p-value of 0.01 for the estimated effect. In the current meta-analysis we have therefore presented the results primarily in a fixed effects model, wherein such conservative methodology is unnecessary. Moreover, the choice of a cut-off value of 0.01 would have conferred insignificant meta-analytic results in the majority of analyses, a case which was rejected by the individual result of each study. We believe that the choice of a p-value of 0.1 in this case resulted in a better match between the clinically and statistically significant differences.

In summary, this meta-analysis confirmed the concept that chronic use of ACE inhibitors is associated with a small but favourable reduction in ventricular volumes — remodelling — in the long-term. This effect is observed especially in patients who are potentially prone to left ventricular dilatation. Based on this small volume improvement observed it is difficult to accept remodelling as the sole explanation for the overall beneficial effect of ACE inhibitors.

5. Limitations of the study

The differences in study design and patient characteristics probably contributed some heterogeneity between the included studies, which to some extent limited the interpretation of the results. Exclusion of some studies could have induced significant selection bias. Publication bias is also possible. Another possible source of bias could be the combination of ventricular volume measurements after different follow-up periods during the same term. Errors associated with echocardiographic measurements in the included studies might also have been reflected in the combined results.

Acknowledgement

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