



# Angiotensin-converting-enzyme inhibitors in hemodynamic congestion: a meta-analysis of early studies

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## Abstract

**Aim** Major clinical trials have shown that angiotensin-converting enzyme (ACE) inhibitors reduce mortality and morbidity in congestive heart failure (HF). Prior to these seminal findings hemodynamic effects of ACE inhibitors were examined in small studies. We aimed to review these studies systematically and meta-analyze the effects of ACE inhibitors on hemodynamics in HF.

**Methods and results** We identified studies investigating the acute hemodynamic effect of ACE inhibitors in naïve patients with congestive heart failure by searching PubMed and the Cochrane Central Register of Controlled Trials. We extracted the changes in hemodynamic measures and their standard errors from study reports or calculated these values from baseline and post-medication measurements. Data were pooled using random effects models. In total, 41 studies with 46 independent cohorts consisting of 676 patients were included. ACE inhibitor treatment reduced pulmonary capillary wedge pressure by 7.3 (95% confidence interval 6.4–8.2) mmHg and right atrial pressure by 3.7 (95% confidence interval 1.3–6.1) mmHg in patients with HF. Cardiac index increased by 0.4 (95% confidence interval 0.2–0.6) ml/min/m<sup>2</sup>. Changes in hemodynamic measures were strongly connected to each other in weighted simple linear regression models.

**Conclusion** Angiotensin-converting enzyme-inhibitors acutely reduced cardiac filling pressures and increased cardiac output in patients with congestive heart failure who were naïve for these drugs. These data indicate that ACE inhibitors exhibit a strong decongesting effect in congestive heart failure. In light of their impact on long-term prognosis, ACE inhibitors should also be considered as decongesting drugs in stable patients.

**Keywords** Heart failure · Congestion · Hemodynamics · Angiotensin-converting-enzyme inhibitors

## Abbreviations

|     |                               |
|-----|-------------------------------|
| ACE | Angiotensin-converting enzyme |
| CI  | Cardiac index                 |
| HF  | Heart failure                 |
| IPD | Individual patient data       |
| MAP | Mean arterial pressure        |

Cor de Wit and Reinhard Vonthein shared senior authorship.

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|      |                                      |
|------|--------------------------------------|
| PCWP | Pulmonary capillary wedge pressure   |
| RAAS | Renin–angiotensin–aldosterone system |
| RAP  | Right atrial pressure                |
| SVR  | Systemic vascular resistance         |

## Introduction

Heart failure (HF) is caused by structural or functional cardiac abnormalities that lead to reduced cardiac output and/or elevated intracardiac pressures. Symptoms and signs like (dyspnea, edema) are direct consequences of these pathophysiologic features [1]. Congestion can be quantified by invasive measurement of right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP) [2, 3]. Its development is multifactorial and not yet fully elucidated. A reduced cardiac output because of systolic dysfunction might elevate filling pressures due to pump effects, but, conversely, such elevated pressures also support contractile force that is related to distension. However, this hemodynamic effect alone may not explain considerable rises in filling pressure. In fact, systolic dysfunction leads to neurohormonal activation characterized by a rise in sympathetic drive, the activation of the renin–angiotensin–aldosterone system (RAAS), and enhanced secretion of arginine vasopressin. Together, these adaptive responses increase systemic vascular resistance, expand the extracellular volume, and reduce venous capacitance which, in turn, worsen congestion as the failing heart is incapable to handle the consequences [4–6].

In 1977, captopril was described as the first inhibitor of the angiotensin-converting enzyme (ACE) and other inhibitors were developed thereafter [7]. ACE inhibitors exert beneficial effects in HF such as improved exercise capacity and left ventricular function [8]. The CONSENSUS trial published more than 30 years ago demonstrated a remarkable reduction of mortality in HF patients treated with enalapril [9]. This, in conjunction with evidence from other studies, led to the proposal that RAAS activation exerts detrimental effects on the failing heart that are independent of concurrent hemodynamic changes [10]. Specifically, angiotensin II exerts hypertrophic and proliferative effects on cardiac cells through AT1 receptors thereby modulating cardiac remodeling.

Early studies considered ACE inhibitors primarily as vasodilators and examined effects on hemodynamics in congestive HF. Since a summary of these studies is lacking, we meta-analyzed studies investigating acute hemodynamic effects of ACE inhibitors in congestive HF to define their early beneficial hemodynamic effects.

## Methods

### Registration, search strategy, and selection of studies

This meta-analysis analysis was registered at PROSPERO (CRD42018087379) on February 1st 2018 and the report follows the PRISMA statement [11].

Studies of potential interest were identified by querying PubMed (last update April 16th 2018) and the Cochrane Central Register of Controlled Trials (last update April 15th 2018). We used three groups of search term and at least one term of each group was required to match: (1) heart failure; (2) pulmonary capillary wedge pressure, pulmonary wedge pressure, or pulmonary artery catheter; (3) ACE inhibitor, captopril, enalapril, lisinopril, ramipril, or trandolapril (see supplement for specific syntax).

Interventional studies (single arm or verum groups of randomized controlled trials) reporting hemodynamic parameters (at least pulmonary capillary wedge pressure) before and after acute treatment with an orally applied ACE inhibitor in patients suffering from congestive heart failure at rest were eligible for inclusion.

After removal of duplicates, title and abstract of identified items were screened independently by two investigators (AJ and AA). Whenever uncertainty remained after screening title and abstract, full-text articles were scrutinized and decision regarding inclusion was made by consent after discussion.

### Data extraction

Data of included studies were extracted independently by two investigators (AJ and AA) using data sheets with uniform coding. Baseline characteristics included number of patients, frequency of New York Heart Association (NYHA) classes, frequency of ischemic heart disease, concomitant medication, utilized ACE inhibitor as well as its dosage regimen and dose. Extracted hemodynamic data included cardiac index (CI), mean arterial pressure (MAP), PCWP, RAP, and systemic vascular resistance (SVR). Chatterjee et al. reported a standard deviation (SD) of 5.1 l/min/m<sup>2</sup> for CI (at a mean of 2.5) after captopril application but we used a SD of 0.5 l/min/m<sup>2</sup> instead of 5.1 for our meta-analysis because the reported SD is most likely a typing error. Only an assumed SD of 0.5 is, in fact, in line with the reported *P* value. Moreover, this SD matches the variance in the control group and variances reported in other studies [12].

### Statistical analysis

Extracted data were transformed to yield the input needed for meta-analysis, i.e., treatment effect TE and its standard

error  $SE_{TE}$ . Treatment effect was defined as mean change in hemodynamic measure from baseline measurement  $b$  (i.e., before ACE inhibitor application) to measurement after drug application indicating the acute effect  $a$ . Most studies reported peak hemodynamic effect for the latter. In case TE was not reported, it was calculated by subtracting  $b$  from  $a$ . Its standard deviation  $SD_{TE}$  was calculated based on the SD of the baseline measurement  $SD_b$ , SD of the measurement after drug application  $SD_a$ , and Pearson's correlation coefficient  $r$  between  $b$  and  $a$  according the following formula:  $SD_{TE} = \sqrt{SD_b^2 + SD_a^2 - 2 \times SD_b \times SD_a \times r}$ .  $SD_{TE}$  was consecutively transformed to  $SE_{TE}$  for further analysis. Pearson's correlation coefficient  $r$  between  $b$  and  $a$  was not published by any included study. However, preliminary literature screening indicated that a couple of authors tabulated individual patient data (IPD) for  $b$  and  $a$ . This enabled us to calculate a study-specific correlation coefficient  $r_{study-specific}$  in these studies. Moreover, a common correlation coefficient  $r_{common}$  was estimated by the restricted maximum likelihood (REML) method in a random effects meta-analysis. This  $r_{common}$  was used to calculate  $SD_{TE}$  for all studies without published  $SD_{TE}$  or IPD to calculate  $SD_{TE}$  as outlined above.

Depending on how data were reported in individual papers, SE was calculated as (a) SD divided by the square root of sample size or (b) confidence interval length divided by two times the quantile of the  $t$ - or normal distribution used and SD was calculated as interquartile range divided by the expected interquartile range of a standard normal sample of the respective size.

Finally, study-specific effect estimates (i.e., using TE and  $SE_{TE}$ ) were pooled by means of a random effects meta-analysis for which between study variance  $\tau^2$  was estimated using the REML method. The  $t$ -distribution following Knapp and Hartung was applied for tests and confidence intervals.

Heterogeneity was assessed using Higgins' and Thompson's  $I^2$  and tested by means of Cochran's  $Q$  statistic. Heterogeneity was expected within studies and across studies due to different populations, different study medications, doses and/or dosage regimens, and follow-up times (i.e., duration between ACE inhibitor application and assessment of  $a$ ). As a consequence, differently treated study arms were considered like different studies in the random effects models. Sources of heterogeneity were explored by subgroup analyses and meta-regression. The following subgroup analyses were pre-specified: specific study medication, dosage regimen, and timing of hemodynamic evaluation (i.e., acute versus long-term effect after weeks to months). The latter was abandoned due to sparse data and this meta-analysis was focused instead on acute effects.

To analyze robustness of our statistical approach, we calculated random effects models using different SE of the treatment effect  $SE_{TE}$  in studies which published IPD: (1)  $SE_{TE}$  derived directly from IPD, (2)  $SE_{TE}$  calculated by

study-specific Pearson's correlation coefficients  $r_{study-specific}$  and (3)  $SE_{TE}$  calculated by the common Pearson's correlation  $r_{common}$ .

Analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria) and its packages *meta* and *metafor*.

## Results

After exclusion of 43 duplicates, our search identified 146 items of potential interest. Of these, 105 were excluded because they did not meet the inclusion criteria. Thus, 41 remaining studies were included in our meta-analysis (Fig. 1). All studies were prospective and published between 1979 and 1997. Supplemental Table 1 summarizes study characteristics. In these studies, different ACE inhibitors were utilized. Captopril was the most frequent ACE inhibitor examined (27 of 41; 66%), followed by enalapril (9 of 41; 22%), and lisinopril (3 of 41; 7%). Perindopril and ramipril were each used in 1 (2%) study. In total, 676 patients with a median of 10 (interquartile range 9–17) patients per study (-arm) were included. Three studies reported independent cohorts treated with different doses (Supplemental Table 1).

### Analyzing individual patient data

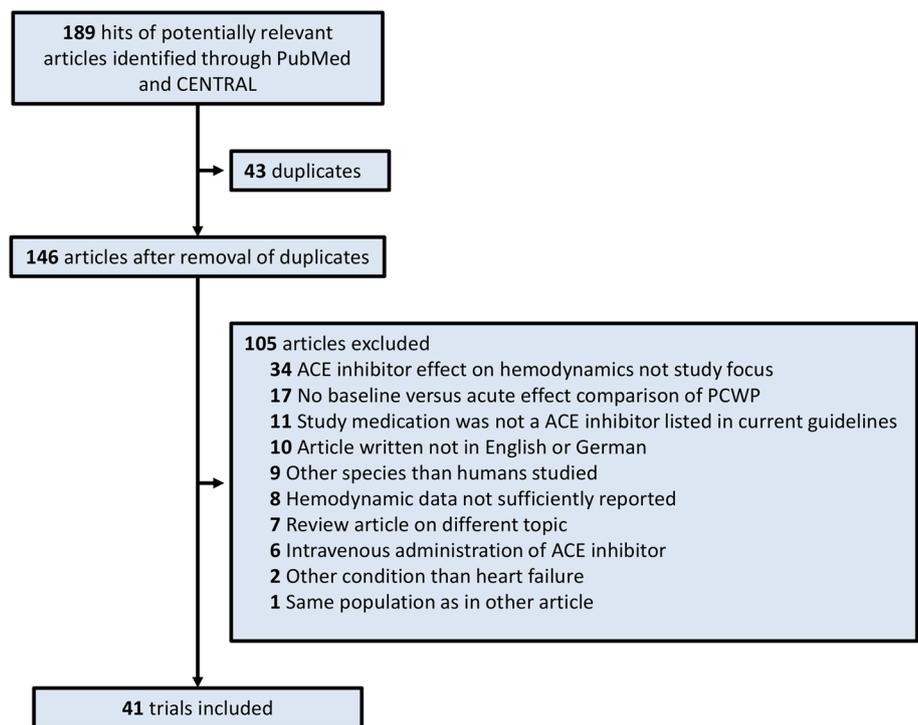
Individual patient data (IPD) for CI, MAP, PCWP, and SVR were reported in 6 of 41 (15%) studies. While 5 of these 6 studies reported also IPD for RAP, this was not done by Nigri et al. [13]. Hence, only 5 of 41 (12%) studies were available for analyzing IPD for RAP. Using these studies accordingly, the common Pearson's correlation coefficient  $r_{common}$  was estimated to be 0.87 for CI, 0.82 for MAP, 0.76 for PCWP, 0.92 for RAP, and 0.83 for SVR. Pooled treatment effects using IPD,  $r_{study-specific}$  and  $r_{common}$  for CI, MAP, PCWP, RAP, and SVR of these studies are listed in Table 1. Effect estimates and corresponding confidence intervals were very similar regardless of the method used to compute  $SE_{TE}$ . Therefore, we felt confident to generalize the common Pearson's correlation coefficients  $r_{common}$  to all studies without  $SD_{TE}$  or IPD to calculate the SE of treatment effect  $SE_{TE}$  for subsequent meta-analyses.

### Analyzing aggregated data

Considering all available cohorts, weighted means at baseline (i.e., before application of an ACE inhibitor) amounted to 87 mmHg for MAP, 24 mmHg for PCWP, 20 mmHg for RAP, and 1747  $\text{dyn} \times \text{s} \times \text{cm}^{-5}$  for SVR. Weighted mean for CI was 2.0 l/min/m<sup>2</sup>.

After treatment with ACE inhibitors, the hemodynamic parameters changed to more beneficial values (i.e., reduced

**Fig. 1** Flowchart shows the identification of included studies. ACE angiotensin-converting enzyme, PCWP pulmonary capillary wedge pressure



**Table 1** Treatment effect considering only studies with published individual patient data

| Hemodynamic parameter             | IPD                   | Formula with study-specific <i>r</i> | Formula with common <i>r</i> |
|-----------------------------------|-----------------------|--------------------------------------|------------------------------|
| CI (l/min/m <sup>2</sup> )        | 0.4 [0.2 to 0.6]      | 0.4 [0.2 to 0.6]                     | 0.4 [0.2 to 0.5]             |
| MAP (mmHg)                        | −13.3 [−20.7 to −5.9] | −13.4 [−20.7 to −6.1]                | −13.4 [−20.9 to −5.9]        |
| PCWP (mmHg)                       | −8.1 [−10.9 to −5.4]  | −8.1 [−10.8 to −5.4]                 | −8.1 [−11.1 to −5.6]         |
| RAP (mmHg)                        | −3.7 [−6.1 to −1.3]   | −3.7 [−6.1 to −1.3]                  | −3.9 [−6.2 to −1.5]          |
| SVR (dyn × s × cm <sup>−5</sup> ) | −538 [−840 to −236]   | −537 [−840 to −234]                  | −412 [−708 to −115]          |

CI cardiac index, IPD individual patient data, MAP mean arterial pressure, PCWP pulmonary capillary wedge pressure, RAP right atrial pressure, SVR systemic vascular resistance

filling pressures, mean arterial pressure, and systemic resistance, but enhanced cardiac output; Table 2). However, visual inspection of forest plots (Fig. 2 for PCWP and supplemental Figs. 1 to 4 for CI, MAP, RAP, and SVR, respectively) as well as the corresponding statistics (i.e., Higgins’ and Thompsons’ *I*<sup>2</sup>) revealed considerable heterogeneity (Table 2).

### Exploring heterogeneity

To explore the large heterogeneity, we performed subgroup analyses and estimated meta-regression models for change in PCWP. Differences between studies using a single dose compared with those using more complex dosing regimens did not explain much heterogeneity (Supplemental Fig. 5; *P* for subgroup difference = 0.06; *I*<sup>2</sup> in each subgroup > 85%). Subdividing studies according to the

applied ACE inhibitor revealed differences between subgroups (Fig. 3; *P* for subgroup difference < 0.001). However, heterogeneity was still high within each subgroup (*I*<sup>2</sup>: 76.5%, 88.4%, 79.1%, and 29.9% for captopril, enalapril, lisinopril, and ramipril, respectively). A large heterogeneity was still observed in meta-regression models adjusted for year of publication, dosing regimen, and ACE inhibitor (Supplemental Table 2). Surprisingly, adjustment for year of publication decreased heterogeneity the most. The bubble plot in Fig. 4 depicts the association between year of publication and treatment effect. This association suggests a decrease of the change in PCWP with time. Considering the cumulative doses of ACE inhibitor applied in the analyzed studies (Supplemental Table 1), it appears that these doses decreased with the year of publication. However, the descriptions of drug application in these studies were too heterogeneous to evaluate this statistically.

**Table 2** Treatment effect and heterogeneity measures considering all studies

| Hemodynamic parameter             | <i>n</i> of cohorts | <i>n</i> of patients | Treatment effect [95% confidence interval] | $I^2$ | $\tau^2$ | <i>P</i> |
|-----------------------------------|---------------------|----------------------|--|-------|----------|----------|
| CI (l/min/m <sup>2</sup> )        | 37                  | 579                  | 0.4 [0.3 to 0.4]                           | 89%   | 0.02     | <0.001   |
| MAP (mmHg)                        | 41                  | 617                  | −14.2 [−16.0 to −12.4]                     | 86%   | 26.3     | <0.001   |
| PCWP (mmHg)                       | 46                  | 676                  | −7.3 [−8.2 to −6.4]                        | 85%   | 7.0      | <0.001   |
| RAP (mmHg)                        | 31                  | 531                  | −2.6 [−3.2 to −2.1]                        | 90%   | 2.0      | <0.001   |
| SVR (dyn × s × cm <sup>−5</sup> ) | 39                  | 611                  | −450 [−521 to −379]                        | 98    | 40,299   | <0.001   |

$I^2$  is a measure of heterogeneity independent of the number of studies analyzed and should be interpreted as percentage variability attributable to heterogeneity between studies.  $\tau^2$  is a measure of between study variance; its square root is measured in the same unit as the outcome. *P* is the *P* value of the test with homogeneity of effects as null-hypothesis

CI cardiac index, MAP mean arterial pressure, PCWP pulmonary capillary wedge pressure, RAP right atrial pressure, SVR systemic vascular resistance

### Associations between hemodynamic measures

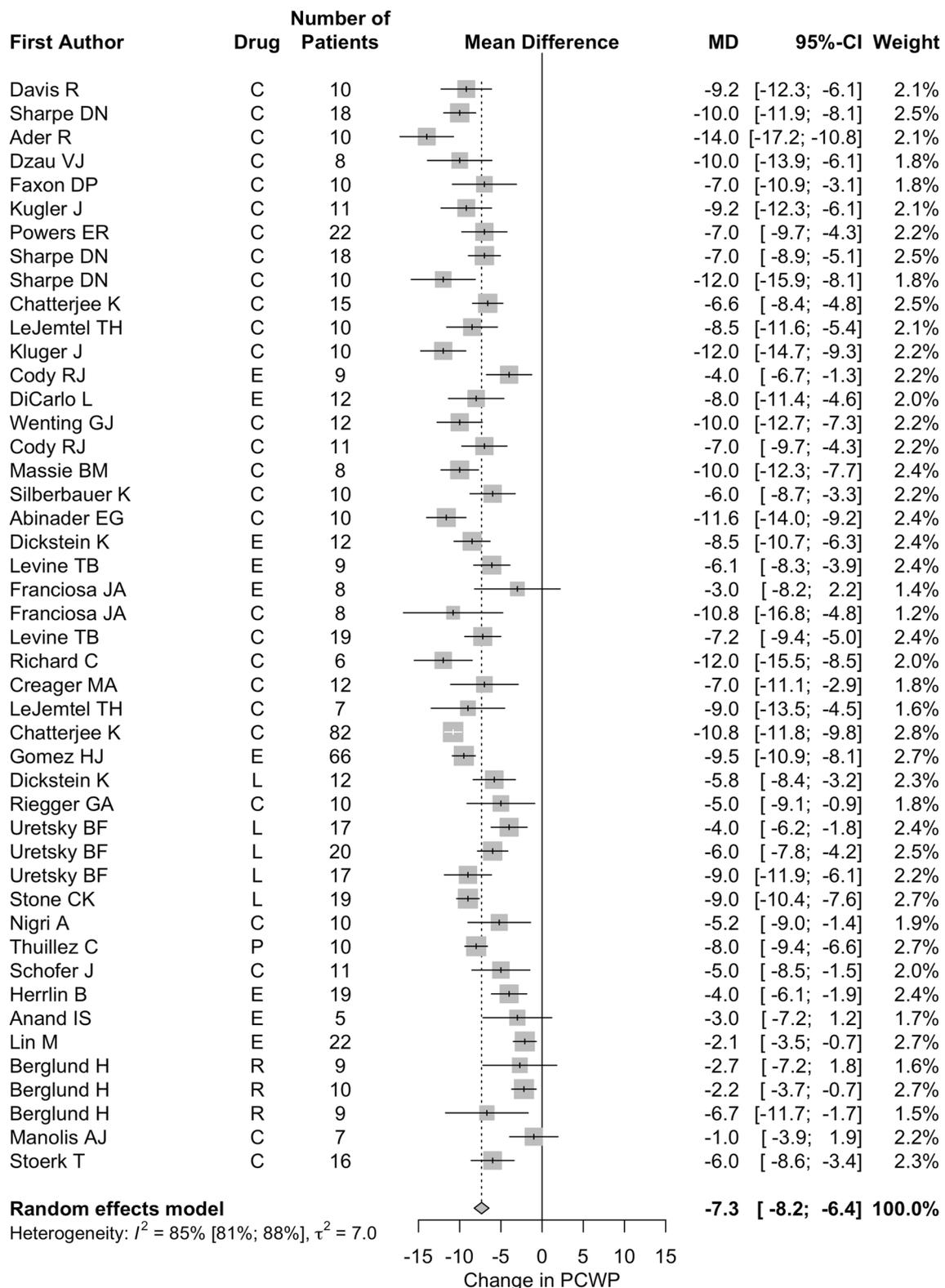
Simple linear regressions weighted by the weights from the random effects meta-analysis of the dependent variable revealed significant associations between hemodynamic parameters, for example decreases in MAP and PCWP were significantly associated (Fig. 5a). Similarly, reductions in right ventricular filling pressure (RAP) and decreases in systemic vascular resistance (SVR) were significantly associated with declines in left ventricular filling pressure (PCWP) after ACE inhibitor treatment (Fig. 5b, c). A negative association was revealed for cardiac index and PCWP, i.e., a stronger decrease in PCWP was associated with larger increases in CI (Fig. 5d).

### Discussion

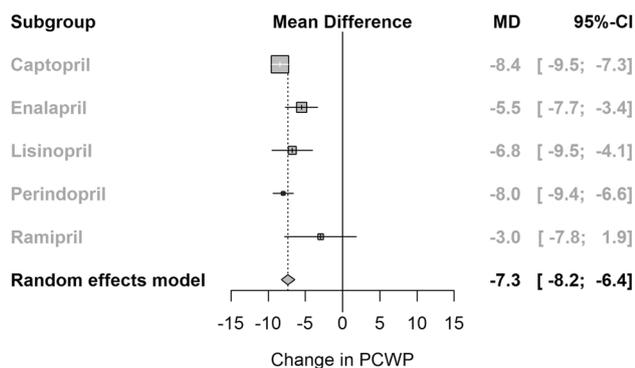
Patients suffering from congestive heart failure without modern guideline-directed medication exhibited elevated cardiac filling pressures (i.e., RAP and PCWP) reflecting hemodynamic congestion and reduced cardiac output (cardiac index) in invasive hemodynamic assessment. Several small studies investigated acute hemodynamic changes upon the start of ACE inhibitor treatment in ACE inhibitor naïve patients. Our meta-analysis of these studies demonstrates that ACE inhibitors consistently decrease filling pressures as well as systemic vascular resistance and, conversely, increase cardiac output. We conclude that ACE inhibitors exhibit acute decongesting properties and relieve filling pressures for both ventricles. At the study level, the decrease in RAP was more pronounced in studies with higher decrease in PCWP suggesting that left- and right-sided filling pressures are closely coupled. While cardiac output increases with enhanced filling pressure and the corresponding distension in the healthy heart, it is well known that in congestive heart failure an increase in filling pressure beyond an inflection point rather deteriorates cardiac output [14]. It is

therefore not surprising that the increases in cardiac index were particularly pronounced in studies with large decrease in PCWP. The strongest effect (i.e., high slope of the association curve together with a very narrow error band) of associations between analyzed parameters in weighted simple linear regression analysis was observed for MAP and PCWP. This suggests that decreases in afterload predict declines in left-sided filling pressure after the start of ACE inhibitor treatment. In fact, substantial decreases in SVR were observed after ACE inhibition and the changes in SVR were also closely associated with PCWP. This implies that indeed the decrease in peripheral vascular resistance due to the abrogation of the vasoconstrictive effect of the RAAS is a major player in the acute decongesting effect of ACE inhibitors. Interestingly, decreases in RAP were likewise associated with decreases in PCWP and may reflect a direct effect of PCWP on pressures in the pulmonary circulation. In addition, a reduction in central sympathetic drive due to ACE inhibition with consecutive dilation of splanchnic veins and venules may also be involved [15]. RAP reduction due to a decrease in the overall extracellular volume as a consequence of less sodium retention is unlikely as RAP reduction is observed rather promptly.

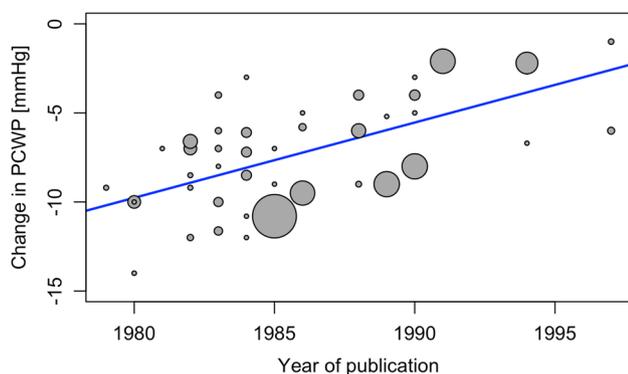
Our meta-analysis of these initial studies investigating hemodynamic effects of ACE inhibitors is important for several reasons. Firstly, ACE inhibitors are known to improve prognosis in HF with regard to all-cause mortality and/or rehospitalization, but their decongesting capability is often neglected. Thus, they are not applied at the target dose or even not prescribed at all in patients with low-normal blood pressure while the same patient is treated with diuretics to control congestion. Although diuretics are important to alleviate congestion and symptoms in decompensated patients, randomized controlled trials have not demonstrated a prognostic benefit of these drugs up to now. Therefore, it might be beneficial for the patient to reduce diuretics in favor of ACE inhibitors after recompensation. Secondly, the analyzed studies built the rationale for major outcome trials



**Fig. 2** Forest plot shows change in pulmonary capillary wedge pressure (PCWP) depicted as mean difference (MD) and its 95% confidence interval (95% CI). C captopril, E enalapril, L lisinopril, P perindopril, R ramipril



**Fig. 3** Forest plot shows change in pulmonary capillary wedge pressure (PCWP) according to angiotensin-converting enzyme inhibitor. Change in PCWP is depicted as mean difference (MD) and its 95% confidence interval (95% CI)



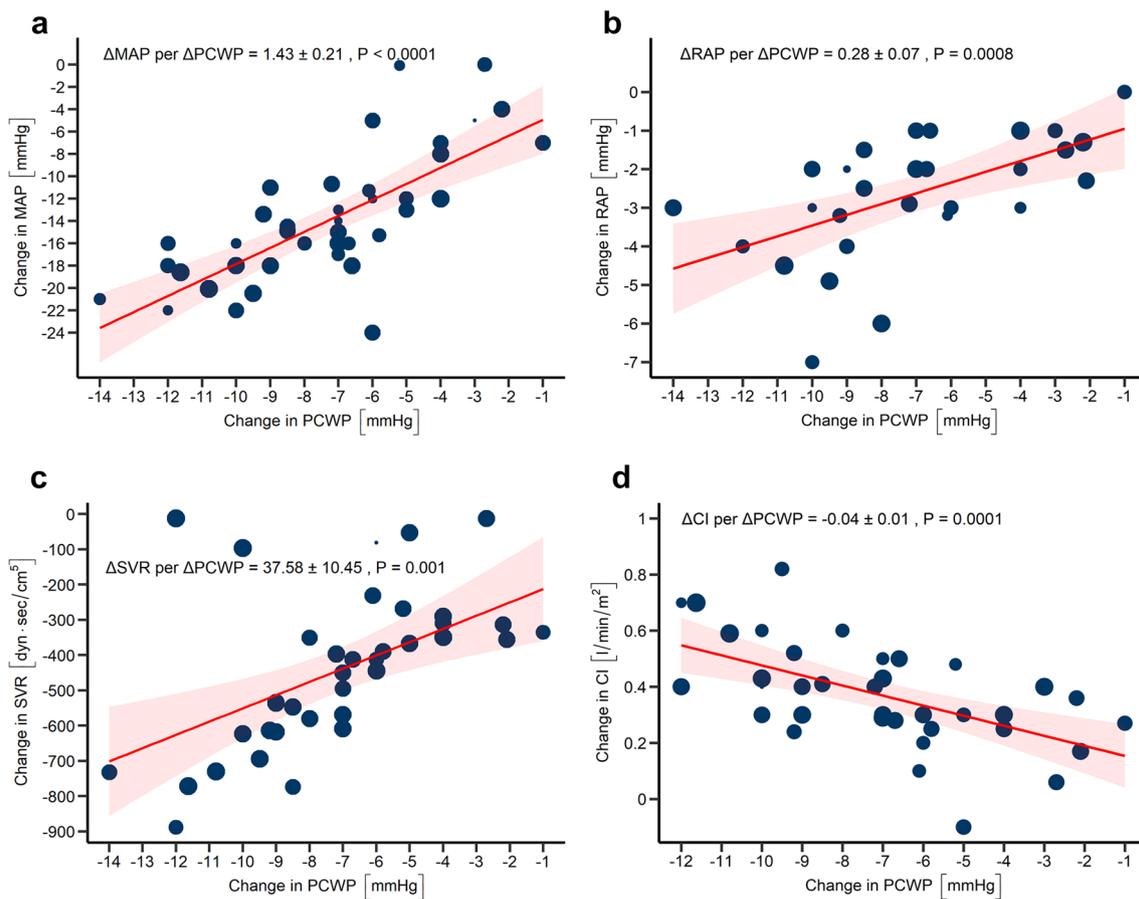
**Fig. 4** Bubble plot shows the relationship between year of publication and change in pulmonary capillary wedge pressure (PCWP). The size of the study is reflected by the size of the bubble. Slope for modification of change in PCWP per year is 0.42 (95% confidence interval 0.26–0.58;  $P < 0.0001$ )

demonstrating that ACE inhibitors reduce mortality in HF patients with reduced ejection fraction [9, 16, 17]. Accordingly, changes of hemodynamic parameters were measured upon treatment with novel vasodilators applied intravenously in patients hospitalized for acute decompensated heart failure. For example, in the Vasodilator in the Management of Acute Congestive heart failure (VMAC) study, nesiritide was superior over nitroglycerin and placebo in improving central hemodynamics (i.e., PCWP, RAP, and CI) [18]. Compared to placebo, ularitide was superior in improving PCWP and CI in SIRUS II [19]. In the Pre-Relax-AHF study, serelaxin decreased systolic blood pressure more than placebo in patients with a baseline systolic blood pressure of 140 mmHg or above [20]. In a subsequent study, serelaxin also proved to attenuate filling pressures (RAP and PCWP) [21]. Taken together, these studies demonstrated favorable hemodynamic effects for these novel intravenous vasodilators and they are in this regard comparable to the ACE

inhibitor studies pooled in our meta-analysis. However, in contrast to ACE inhibitors, all consecutive outcome trials investigating these vasodilator drugs failed to demonstrate a benefit on hard endpoints despite prior evidence for relieving hemodynamic congestion [22–24]. This discrepancy may be reconsidered as follows: Firstly, most cases of so-called acute decompensated HF are rather progressive deteriorations of chronic HF and filling pressures most likely rose already long before hospitalization [25]. By that time, congestion-related end-organ damage may have already occurred, and even immediate treatment with a novel vasodilator may not limit the process at this stage. Secondly, duration of treatment was rather short 48 h in RELAX-AHF [20] and TRUE-AHF [23]; 24–168 h in ASCEND-HF [22], whereas ACE inhibitors were prescribed for months to years in major outcome trials [9, 16, 17]. The treatment duration of the studies included in our meta-analysis on ACE inhibitors was also rather short but sufficiently long to elicit beneficial hemodynamic changes. Combining this information, one might speculate that early hemodynamic improvements are not relevant for prognosis if not sustained. Alternatively, ACE inhibitors may exert indeed an additional benefit through not-well defined long-term effects on neurohumoral activation in HF that are unrelated to hemodynamic improvement by decongestion. This may also include so-called pleiotropic effects that are more beneficial in case of ACE inhibitors than in these novel agents. Nevertheless, the present study verifies an acute decongesting effect of ACE inhibitors that may support the efficacy of ACE inhibitor therapy and this effect should be kept in mind when deciding between diuretics or ACE inhibitors. Our meta-analysis comprised in total 667 patients only. From today's perspective, it is amazing that such small studies (the largest enrolled 82 patients) were sufficient to establish a new therapeutic concept and were acceptable as the basis to organize larger outcome trials.

## Limitations

All pooled analyses comprise a large heterogeneity. We were not able to explain a high degree of the heterogeneity by means of subgroup analyses or meta-regression analyses. Nevertheless, we believe that much heterogeneity is introduced by different study protocols and specifically by different dosing regimens although we were unable to verify this assumption statistically. Dosing regimens were not always reported in enough detail to allow further subgroup analyses. For example, a meta-regression on cumulative ACE inhibitor dose would be interesting, but was not possible due to insufficient reporting. Moreover, doses were escalated in some studies until a certain target effect was achieved which led to different dosages for different patients within the same study. Another major contributor



**Fig. 5** Scatterplots show the association between mean difference of pulmonary wedge pressure (PCWP) and **a** mean arterial pressure (MAP), **b** right atrial pressure (RAP), **c** systemic vascular resistance

(SVR), or **d** cardiac index (CI) on the study level. Each dot represents a single study, dot size illustrates weight of the respective study in linear regression analysis

to heterogeneity is the fact that we meta-analyzed small studies for which it is known that they are more heterogeneous than larger studies [26].

## Conclusions

ACE inhibitors reduced cardiac filling pressures, mean arterial pressure as well as systemic vascular resistance and increased cardiac output in patients with congestive HF who were naïve for ACE inhibitors. Changes in hemodynamic measures were strongly associated on a study level and these associations will most likely also hold true on the patient-level. Therefore, we suggest that ACE inhibitors should also be regarded as decongesting drugs in stable heart failure patients and be considered primarily instead of diuretics for this purpose in light of the long-term beneficial effect.

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## Compliance with ethical standards

**Conflict of interest** No conflict of interest.

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