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RESEARCH ARTICLE

Sex differences of angiotensin-converting enzyme inhibitors in blood pressure lowering and cardiac remodeling: a systematic review and meta-analysis

Sophie A. J. S. Laven[1], MD; Daniek A. M. Meijs[1], MD; Zenab Mohseni-Alsalhi[1], MSc; Eveline M. van Luik[1], BSc; Maud A. M. Vesseur[1], MD; Esmée W. P. Vaes[1], BSc; Nick Wilmes[1], MD; Sander de Haas[1], MSc MD; Marc E. A. Spaanderman[1,2], MD PhD; Chahinda Ghossein-Doha[1,3], MD PhD

[1]Department of Obstetrics and Gynecology, Maastricht University Medical Center (MUMC+), the Netherlands;
[2]Department of Obstetrics and Gynecology, Radboud University Medical Center, the Netherlands;
[3]Department of Cardiology, Maastricht University Medical Center (MUMC+), the Netherlands;

*lavensophie@gmail.com

ABSTRACT

Objectives: Hypertension is the leading risk factor for cardiovascular disease. While treatment of high blood pressure is essential in cardiovascular disease prevention or slowing it down once cardiovascular disease occurred, it is assumed that pharmacological effectiveness may be hampered by sex differences. The aim is to evaluate sex-stratified effects for angiotensin-converting-enzyme inhibitors (ACEIs) on blood pressure and cardiac function in hypertensive participants.

Methods: A systematic review and meta-analysis were performed for studies on ACEIs from 1945 to May 2020. Studies had to present both baseline and follow-up measurements of the interested outcome variables and present sex stratified data. Mean differences were calculated using a random-effects model. 45 studies with 976 participants were used in this review.

Results: In females as compared to males, systolic blood pressure decreased by 19.9 mmHg (95% CI, -26.8; -13.0) vs. 15.1 mmHg (95% CI, -19.5; -10.8), diastolic blood pressure by 14.5 mmHg (95% CI, -17.2; -11.8) vs. 8.5 mmHg (95% CI, -11.4; -5.7), heart rate by -3.5 bpm (95% CI, -6.1; -0.9) vs. -2.5 bpm (95% CI, -4.8; -0.2). Only diastolic blood pressure lowered significantly more in females as compared to males. Left ventricular ejection fraction increased by 2.3% (95% CI, 0.8; 3.7) vs. 1.5% (95% CI, 0.6; 2.3), but without reaching statistical significance.

Conclusion: Although hypertensive treatment effects of ACEIs are comparable between sexes, diastolic blood pressure response is stronger in females, which may guide treatment choices in systolic or diastolic hypertension. It may be that other pharmacological different antihypertensive compounds show sex-specific differences in effectiveness.

KEYWORDS: hypertension; cardiovascular disease; antihypertensive drugs; angiotensin-converting-enzyme inhibitors; sex differences

Introduction

Cardiovascular disease (CVD) is responsible for approximately one third of all deaths above the age of 35 years[1] and is the leading cause of morbidity and mortality worldwide[2,3]. Today, in western countries more females than males die of CVD[4-6] and this mortality rate, specifically among younger females, is increasing[7]. Several underlying causes for this public health issue exist, including the misdiagnosis of CVD in females, which may lead to insufficient treatment and a poorer prognosis[8]. This may be the consequence of lacking sex-specific evidence due to female underrepresentation in clinical trials and the former belief that CVD predominantly affects males[9]. Besides, females present CVD approximately a decade later than males, most likely as at least partly a consequence of the attenuation of the protective effects of estrogen[9]. These factors could result in suboptimal awareness and with it hypertension-related adverse events in females[10].

Antihypertensive medication is the most effective blood pressure (BP) decreasing therapy and has proven to hamper future development of CVD[10]. Angiotensin-converting-enzyme inhibitors (ACEIs), one of the major antihypertensive drug classes, have clinically been proven effective and are recommended in current guidelines as first-line antihypertensive treatment[11]. They exert their effect by blocking angiotensin-converting enzyme that transforms angiotensin I to angiotensin II, and in this way interfere with the renin-angiotensin-aldosterone system (RAAS)[12]. Sex specific differences, related to the effects of estrogen on RAAS, have been linked to distinct pharmacokinetics of ACEIs in both sexes[13]. However, treatment effects of ACEIs have mostly been investigated in males and current sex-neutral treatment recommendations can therefore be questioned in their effectiveness and prevention of CVD in females[10,14]. Current trials have sparsely studied treatment effects of ACEIs sex-specifically which makes identical efficiency arguable. Therefore, this systematic review and meta-analysis aimed to study the intervention effects of ACEI treatment on cardiovascular and hemodynamic variables in female compared to male adults.

Methods

SERIES OF META-ANALYSIS:

The search, inclusion and exclusion criteria are developed for a series of systematic reviews and meta-analyses to assess the effect of the five major groups of antihypertensive drugs on cardiovascular outcomes in females specifically, as compared to males. The current systematic review and meta-analysis investigates the effect of ACEIs. Our review was registered in Prospero database with registration number: CRD42021273583.

LITERATURE SEARCH:

A literature search was conducted in PubMed (NCBI) and EMBASE (Ovid) for studies evaluating the effects of antihypertensive medication on cardiovascular and hemodynamic variables in hypertensive individuals. First, title and abstract of the studies were assessed by two independent researchers. Second, full-text screening was performed during which data on important baseline and demographic variables, intervention characteristics, blood pressure (BP), and cardiac function outcome variables were extracted.

The search included all publications from inception (1945) up to May 2020. The search strategy focused on cardiac geometry, heart failure, diastolic dysfunction, myocardial infarction and cerebrovascular accident (CVA) as detailed in the supplements (Table S1). The search limits used were 'humans' and 'journal article'. The search served to study two objectives:

To determine the representation of females in studies on the effect of antihypertensive drugs on CVD for the past century.

To study differences and similarities between females and males in the effect of antihypertensive medication on BP, cardiac function, and geometry.

ELIGIBILITY CRITERIA:

Studies had to focus on acute (0-14 days), subacute (15-30 days) and/or chronic (>31 days) effects of antihypertensive therapy with at least one type of ACEI in female and/or male adults (≥18 years) diagnosed with hypertension in presence or absence of CVD. Moreover, studies had to include a mean with standard deviation (SD), standard error (SE), or 95% confidence interval (95% CI) of the baseline and follow-up measurements of one of the predefined variables systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR), left ventricular ejection fraction (LVEF), left ventricular mass (LVM) and/or EA ratio. Studies also had to report the mean dose or dose range and treatment duration. The antihypertensive treatment had to be compared to a reference group (control, placebo or antihypertensive medication group). Mean values with SD were requested from the authors by email if articles presented their data differently (for example, median with interquartile range). All study designs which report a baseline and follow-up measurement were included in this systematic review.

STUDY SELECTION:

After the initial search, studies were screened based on title and abstract. During this selection, other systematic reviews and meta-analyses, literature reviews, case reports, animal studies, and in vitro studies were excluded. Studies with subjects younger than 18 years and articles in another language than English or Dutch were excluded as well. The remaining studies were screened for suitability based on full-text using the eligibility criteria. Studies were excluded if outcomes were not separated by antihypertensive medication (if participants received more than one antihypertensive medication as intervention) or if the exact treatment duration, mean dose or dose range for the antihypertensive medication were not specifically reported. Studies with individuals undergoing invasive operations, performing exercise during measurements, or undergoing dialysis or chemotherapy were excluded as well. In case the articles did not separate outcomes for females and males, but all other eligibility criteria were met, authors from articles published in 1980 and later were e-mailed or approached via research gate to request sex-specific data. E-mail addresses from either the first author, corresponding author, or head of the department were retrieved from corresponding details in the article, research gate or world wide web searching for their name or institution. If authors did not respond within two weeks, a reminder was sent. If no contact details were found or if authors did not respond within

three weeks after sending a reminder, the article was excluded from the systematic review. The reason for exclusion was registered for the full-text selection. Both selection steps were performed in pairs in a blinded standardized manner (title-abstract pairs: MA-EV, CD-SL, EL-DM, ZM-JW, MV-NW; full-text pairs: CD-NW, EL-MV, DM-SL, EV-JW). Discrepancies were resolved by mutual agreement.

DATA EXTRACTION:

Study characteristics (sample size, control group, study design), anthropometric data (age, ethnicity), intervention characteristics (dose, duration, method of measurement), and effect measures mean and SD at baseline and after ACEI intervention of SBP and DBP an MAP, HR, LVEF, and LVM were collected in a predesigned format made by the investigators. The study results were separately extracted for females and males. In this systematic review, only BP data measured via non-invasive methods were extracted. For the other variables, multiple methods were allowed. Data extraction was performed by two investigators (RA, LK). This step of the process was not performed in duplicate.

QUALITY ASSESSMENT:

The included studies were assessed for quality and risk of bias using the Cochrane recommended Risk of Bias 2 (RoB2) tool[15]. Studies were scored with "Low risk of bias", "Some concerns" or "High risk of bias" on five domains including randomization process, deviations from intended interventions, missing data, outcome measurement, and data reporting. To receive an overall risk-of-bias judgement of "Low risk of bias", all domains had to score "Low risk of bias". To receive an overall judgment of "High risk of bias", at least one of the domains was rated as such. All other domain score combinations would rate a study with an overall judgement of "Some concerns". The quality assessment was performed by two reviewers (RA, LK) and differences were solved by a third independent reviewer (DM, SL).

STATISTICAL ANALYSIS:

If a SE or 95% CI was reported in the article, the SD was calculated according to the Cochrane Handbook for Systematic Review of Interventions[16]. Changes in the cardiovascular and hemodynamic variables from baseline were separately analyzed for females and males using a random-effects model as described by DerSimonian and Laird[17]. Because the included studies had some variation in study population and design, the random-effects model was chosen to account for this interstudy variation[17]. Egger's regression test for funnel plot asymmetry was conducted to test for publication bias for each cardiovascular variable[18]. The primary outcome was the mean difference and 95% CI between baseline and follow-up data of the intervention, visualized in forest plots. The relative change from baseline in percentage including 95% CI was also calculated and reported in parentheses behind the mean difference in the text. The I^2 statistic, the ratio between heterogeneity and variability, was calculated as a measure of consistency and expressed as percentage in the forest plots. I^2 is able to distinguish heterogeneity in data from solely sampling variance[19]. Interpretation of I^2 was based on the guidelines in the Cochrane Handbook for Systematic Review of Interventions[20]. Sources of clinical heterogeneity (type, treatment duration, and dosage) and

methodological heterogeneity (quality of study) were investigated by meta-regression analyses using a mixed-effects model[19]. For the meta-analyses and meta-regression analyses, the meta package in the statistical program R version 4.0.3. was used[21,22].

Results

STUDY SELECTION:

The literature search resulted in 73,867 unique studies after removal of duplicates from both PubMed and Embase (Figure 1). A first screening based on title and abstract yielded 15,130 eligible articles for full-text screening. Of these full-text assessed studies, 14,916 (98.6%) matched at least one exclusion criterium. For 766 articles (5%) it was not possible to find or access the full text at the university library or online. 1,141 articles (8%) had an unsuitable study design. This criterium was met when for example only measurements were taken during exercise, or SBP and DBP were measured intravenously. 1,058 articles (7%) did not report original research data, these articles were reviews for example. In 1,886 articles (13%) no antihypertensives were given to the patients participating. In 2,141 articles (14%) antihypertensives were given, but treatment results were not stratified by those. 1,949 articles (13%) were excluded because treatment results were not stratified by sex. 153 articles (1%) did not have reference measurements. 3,864 articles (26%) did not contain any measurements of interest. In 536 articles (4%) data was not suitably reported. In 984 articles (6%) there was no information provided regarding either dose, duration, or both. Finally, there were 438 articles (3%) excluded because of other complications. Remaining articles containing sex-stratified data were eligible for inclusion. Ultimately, a total of 214 articles on hypertension treatment could be included of which 45 articles comprised ACEIs[23-67].

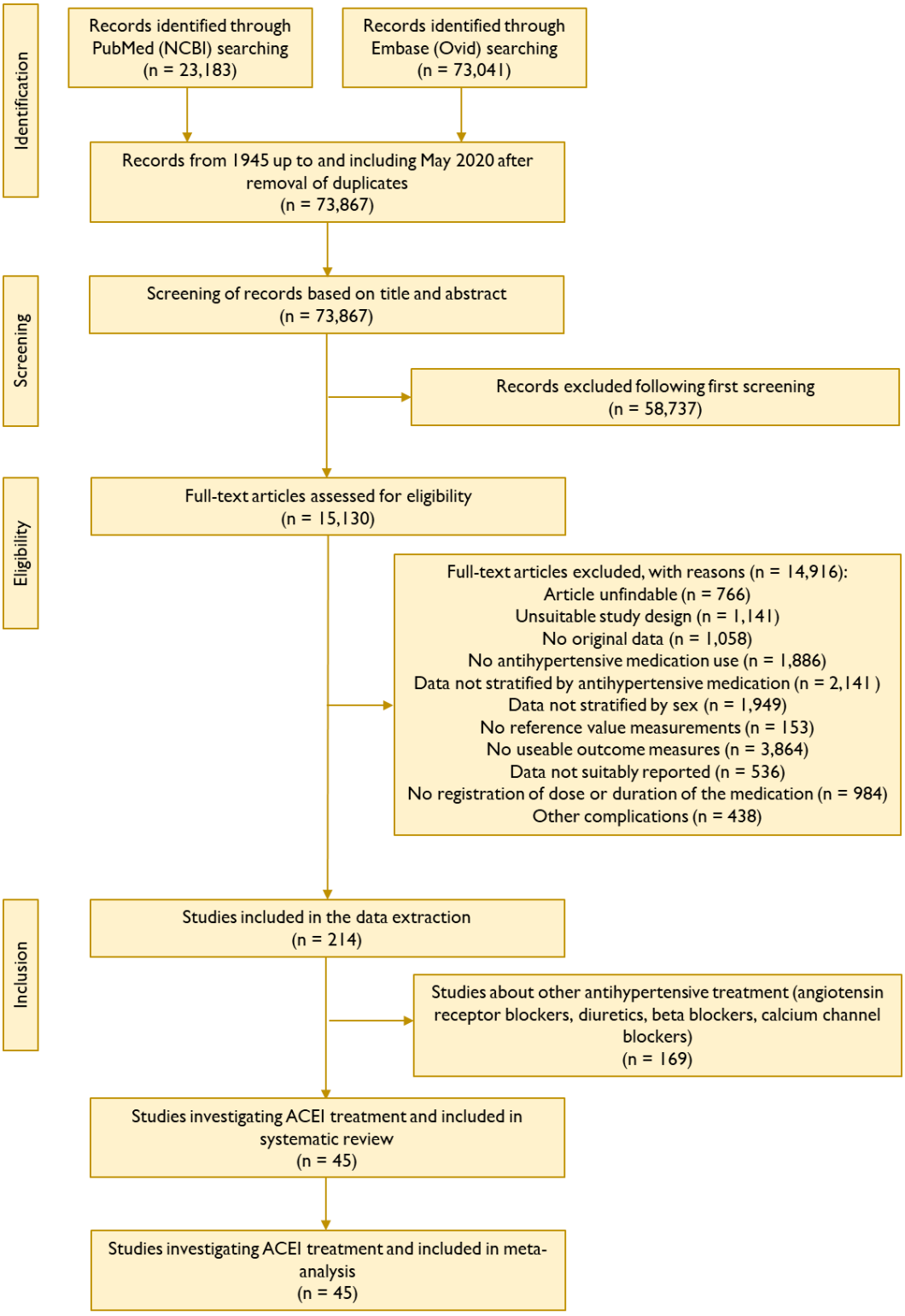

Figure 1 flowchart of systematic selection process

STUDY CHARACTERISTICS:

Study characteristics and anthropometric data are visualized in Table 1 (appendix). Data of 976 subjects using ACEIs were included in this meta-analysis, of whom 201 (21%) were female. The mean age of the subjects from the included studies was 53.64 ± 9 (SD) years.

16 studies analyzed the effects of captopril[25-31,41,46,50,52-54,59-61], 14 of enalapril[23,24,34,35,38-

[40,47,51,57,58,64,65,67], four of quinapril[33,36,43,66], three of lisinopril[32,42,45] and two of perindopril[49,62], cilazapril[44,55] and ramipril[63,68], respectively. One study reported on imidapril and perindoprilat, respectively[37,56].

Heart rate (HR) was studied in 31 studies[23-30,32,34,36,40,42,44-47,49-63,66-68], SBP in 18 studies[23,24,32-47,68], DBP in 18 studies[23,24,32-35,37-47,68], LVEF in 17 studies[23-30,32,34,36,40,42,44-46,49,51,52,54-63,66,67], MAP in 9 studies[23-31], and LVM in four studies[26,39,41,45].

Acute effects of the administered ACEI were evaluated in 11 studies, corresponding to a follow-up period of less than 14 days[25-27,31,44,50,52,53,56,60,61]. Five studies considered the subacute effects, which indicates a follow-up between 15 and 30 days[33,41,43,58,64]. Chronic effects of ACEI treatment were measured in 25 of the included studies, which means a follow-up period of 31 days or longer[23,24,30,32,34-40,42,45-47,49,51,55,59,62,63,65-68]. Two studies measured acute as well as chronic effects[28,29]. One study measured acute as well as subacute effects and acute, subacute and chronic effects, respectively[54,57].

Study designs consisted of 22 randomized controlled trials[23-25,32-36,38,41-45,47,56,58,62,64,65,67,68] of which six had also a crossover design[25,42-44,58,64], and 17 prospective cohort studies[49,52,54,59-61,63,66]. Of the remaining studies, three were cross-sectional studies[26,37,53], one was a retrospective study[55], one was a case-control study[50] and another one was a cohort study[51].

Of the included articles containing ACEI interventions, 28 studies included only male subjects[25-31,33-36,38,41-47,55-61,66,67], 17 studies contained subjects of both sexes[23,24,32,37,39,40,49-54,62-65,68] and none of the studies included only female subjects. Of the studies containing subjects of both sexes, seven studies did not report the outcomes separated for sex[24,32,49,62-64,68] and sex-specific data were therefore requested via email. Ten studies presented the data stratified for sex[23,37,39,40,50-54,65]. Publication bias assessed via Eggers's regression showed significant bias for HR, but no significant bias for all of the other variables included (Table S2).

QUALITY ASSESSMENT:

The quality assessment per domain according to the RoB2 tool is summarized in Figure S2. 22 studies had a high overall risk of bias[24,26,28,37-40,45-47,49-52,54,57-59,62,63,66,68]. 12 out of 45 articles had a low overall risk of bias[23,25,32-35,41-44,56,64]. The remaining 11 studies were scored as having some concerns[27,29-31,36,53,55,60,61,65,67]. The non-randomized controlled trial studies had a high risk of bias due to lacking of randomization and blinding[26,28,37,39,40,46,49-52,54,57,59,63,66].

MEAN ARTERIAL BLOOD PRESSURE:

MAP in the studies population was 104 ± 12.1 (SD) mmHg in females and 101.2 ± 13.6 (SD) mmHg in males (p-value = 0.224). The absolute mean difference and relative change (%) from baseline for MAP are reported in Table 2 and Figure 3. In females as compared to males, MAP decreased 4.9 mmHg (95% CI, -13.1; 3.4)) (-4.7% (95% CI, -12.6; 3.2)) versus 7.1 mmHg (95% CI, -10.4; -3.9) (-7.4% (95% CI, -10.7.; -4.1)) (p-value = 0.615), respectively. Heterogeneity was high in both female (I^2 = 60%) and male (I^2 = 53%) data. The change in MAP was not significantly affected by clinical and methodological sources of heterogeneity (Table 3).

The mean difference for MAP by treatment duration is reported in Table 4. In both

females and males, chronic ACEI treatment effects are comparable (Figures S4, S5), an observation also in line with the calculated effect in time by meta-regression analysis (Figure 21).

Table 2 Pooled changes in cardiovascular and hemodynamic parameters for females and males

Parameter		Females	Males
MAP (mmHg)	MD	-4.9 (-13.1; 3.4)	-7.1 (-10.4; -3.9)
	%	-4.7 (-12.6; 3.2)	-7.4 (-10.7.; -4.1)
SBP (mmHg)	MD	-19.9 (-26.8; -13.0)	-15.1 (-19.5; -10.8)
	%	-13.2 (-17.8; -8.6)	-10.3 (-13.2; -7.3)
DBP (mmHg)	MD	-14.5 (-17.2; -11.8)	-8.5 (-11.4; -5.7)
	%	-15.6 (-18.5; -12.8)	-9.2 (-12.2; -6.2)
HR (bpm)	MD	-3.5 (-6.1; -0.9)	-2.5 (-4.8; -0.2)
	%	-4.8 (-8.3; -1.2)	-3.4 (-6.2; -0.3)
LVEF (%)	MD	2.3 (0.8; 3.7)	1.5 (0.6; 2.3)
	%	5.2 (1.8; 8.6)	3.5 (1.5; 5.5)
LVM (g)	MD	-24.7 (-59.2; 9.7)	-3.6 (-30.7; 23.6)
	%	-13.3 (-31.9; 5.2)	-1.4 (-12.3; 9.4)

Values are reported as mean difference (MD) and relative change (%) compared to baseline with 95% CI. MAP = mean arterial pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, LVEF = left ventricular ejection fraction, LVM = left ventricular mass.

Table 3 P-values of meta-regression analysis

Sources of heterogeneity	MAP	SBP	DBP	HR	LVEF	LVM
Cilazapril	-	0.0054	0.2752	0.6586	0.7662	-
Enalapril	0.2035	0.4472	0.0816	0.7442	0.0017	0.8297
Imidapril	-	0.9126	0.1781	-	-	-
Lisinopril	-	0.2495	0.0868	0.8594	0.9739	0.9228
Quinapril	-	0.2031	0.0868	0.8582	-	-
Ramipril	-	0.8617	0.1279	<0.0001	0.0056	-
Perindopril	-	-	-	0.2493	0.0016	-
Low quality	0.5760	0.2238	0.2647	0.1191	0.2274	0.8381
Moderate quality	0.4367	0.1101	0.2285	0.1078	0.3451	-
Treatment duration	0.4332	0.0015	0.0192	0.1385	0.5060	0.1644
% max dose	0.8148	0.9928	0.6768	0.9001	0.9525	0.9485

Table 4 Pooled changes in cardiovascular and hemodynamic parameters by treatment duration for females and males

Parameter		Females	Males
MAP (mmHg)	MD acute	-	-8.0 (-12.8; -3.1)
	MD subacute	-	-
	MD chronic	-4.9 (-13.1; 3.4)	-6.3 (-11.0; -1.7)
SBP (mmHg)	MD acute	-	-18.3 (-38.6; 2.1)
	MD subacute	-	-10.1 (-12.6; -7.6)
	MD chronic	-19.9 (-26.8; -13.0)	-15.4 (-20.1; -10.7)
DBP (mmHg)	MD acute	-	-7.2 (-15.7; 1.3)
	MD subacute	-	-6.1 (-7.6; -4.6)
	MD chronic	-14.5 (-17.2; -11.8)	-9.0 (-12.4; -5.6)
HR (bpm)	MD acute	0.0 (5.7; 5.8)	-2.2 (-3.7; -0.6)
	MD subacute	-	-6.0 (-33.4; -21.4)
	MD chronic	-4.3 (-6.9; -1.6)	-9.0 (-12.4; -5.6)
LVEF (%)	MD acute	1.6 (-15.4; 18.6)	4.9 (2.3; 7.5)
	MD subacute	4.0 (-6.4; 14.4)	-1.0 (-8.4; 6.4)
	MD chronic	2.2 (0.6; 3.8)	1.3 (0.9; 1.7)
LVM (grams)	MD acute	-	-
	MD subacute	-	-
	MD chronic	-24.7 (-59.2; 9.7)	-3.6 (-30.7; 23.6)

Values are reported as mean difference (MD) compared to baseline with 95% CI. Acute = 0-14 days, subacute = 15-30 days, chronic = >31 days, MAP = mean arterial pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, LVEF = left ventricular ejection fraction, LVM = left ventricular mass.

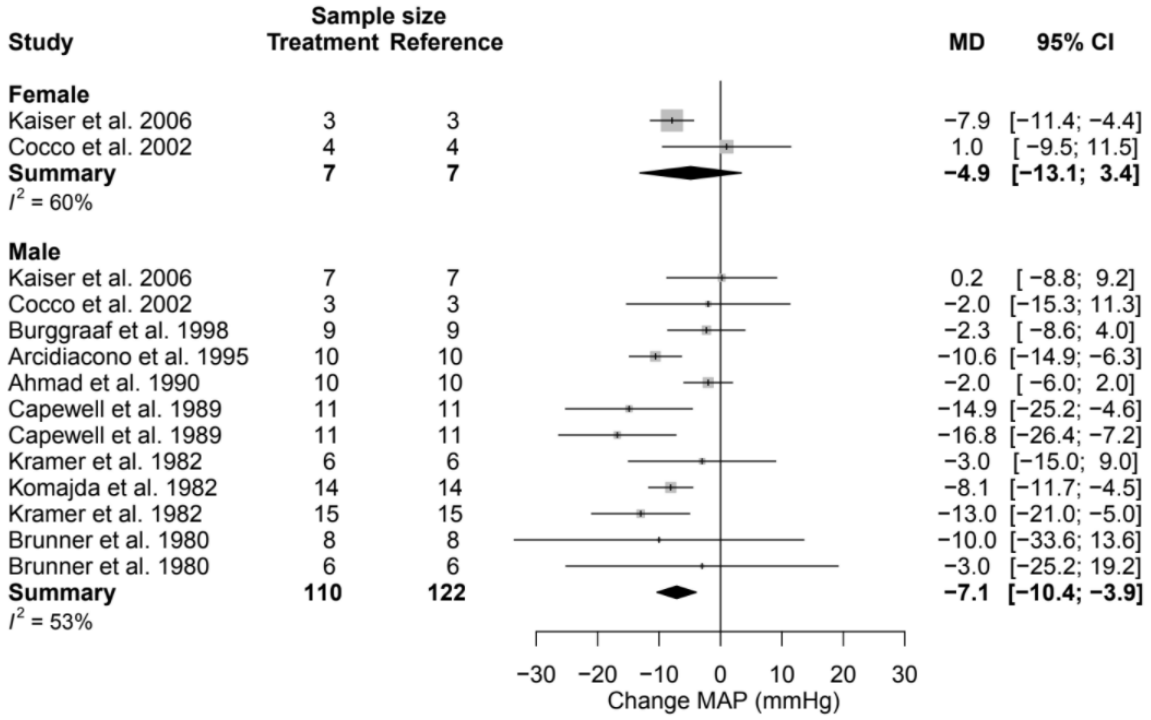

Figure 3 Forest plot of mean arterial pressure (MAP) change in mmHg after ACEI use compared to baseline for females and males. MD = mean difference

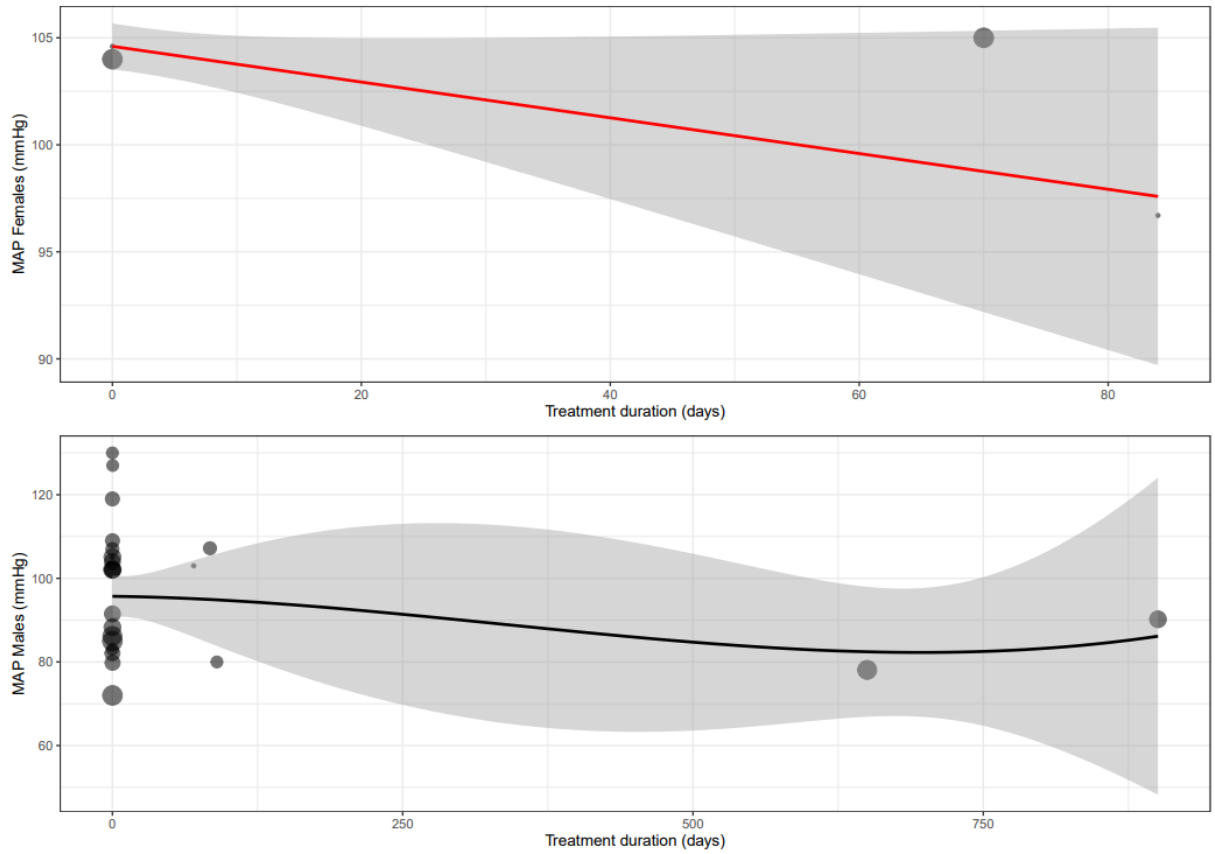

Figure 21 Meta-regression curve of mean arterial pressure (MAP) by treatment duration (days). Every circle is representing one article and the size represents the amount of participants included in the study, shown as a small or larger circle.

SYSTOLIC BLOOD PRESSURE:

The mean SBP in the study population was 152.8 ± 25.4 (SD) mmHg in females and 137.4 ± 10.4 (SD) mmHg in males (p-value = 0.280). SBP decreased significantly by 19.9 mmHg (95% CI, -26.8; -13.0) (-13.2% (95% CI, -17.8; -8.6)) in females as compared to 15.1 mmHg (95% CI, -19.5; -10.8)) (-10.3% (95% CI, -13.2; -7.3)) in males (Table 2, Figure 6). This change would not statistically significant between the sexes (p-value = 0.255). Heterogeneity was high in both female (I^2 = 77%) and male (I^2 = 86%) data. A clinical source of heterogeneity detected by meta-regression analyses was a difference in antihypertensive compound, namely cilazapril (Table 3), which causes a smaller effect. The treatment duration, a methodological source of heterogeneity, did also contribute significantly to the observed change in SBP (Table 3).

The mean difference for SBP by treatment duration is reported in Table 4. In both females and males, chronic ACEI treatment effects are comparable (Figures S7, S8), which is also in line with the calculated effect in time by meta-regression analyses (Figure 22).

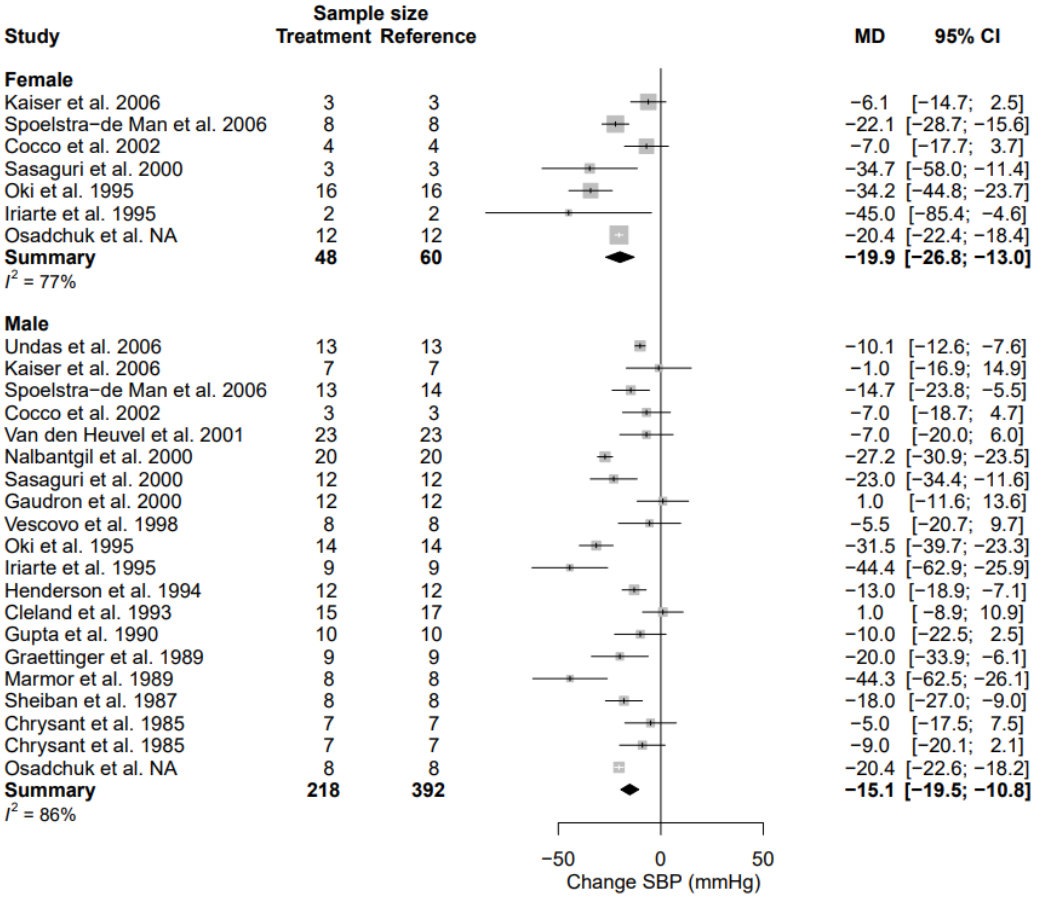

Figure 6 Forest plot of systolic blood pressure (SBP) change in mmHg after ACEI use compared to baseline for females and males. MD = mean difference

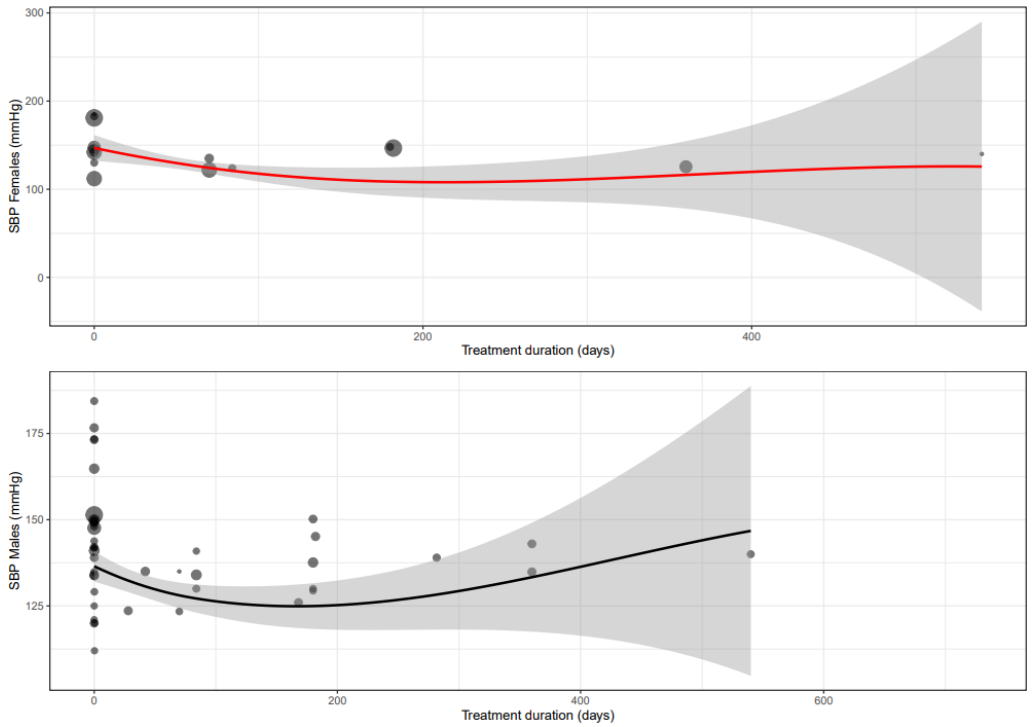

Figure 22 Meta-regression curve of systolic blood pressure (SBP) by treatment duration (days). Every circle is representing one article and the size represents the amount of participants included in the study, shown as a small or larger circle.

DIASTOLIC BLOOD PRESSURE:

The mean DBP in the studies population was 89.7 ± 13.9 (SD) mmHg in females and 91.1 ± 11.4 (SD) mmHg in males (p-value = 0.397). DBP decreased significantly by -14.5 mmHg (95% CI, -17.2; -11.8) (-15.6% (95% CI, -18.5; -12.8)) in females as compared to -8.5 mmHg (95% CI, -11.4; -5.7) (-9.2% (95% CI, -12.2; -6.2)) in males (Table 2, Figure 9). This change was statistically significant between sexes (p-value = 0.003). Heterogeneity was low in female (I^2 = 35%) and high in male (I^2 = 93%) data. Treatment duration contributed significantly to the observed change in DBP (Table 3).

The mean difference for DBP by treatment duration is reported in Table 4. In both females and males, chronic ACEI treatment effects are comparable (Figures S10, S11), an observation also in line with the calculated effect in time by meta-regression analysis (Figure 23).

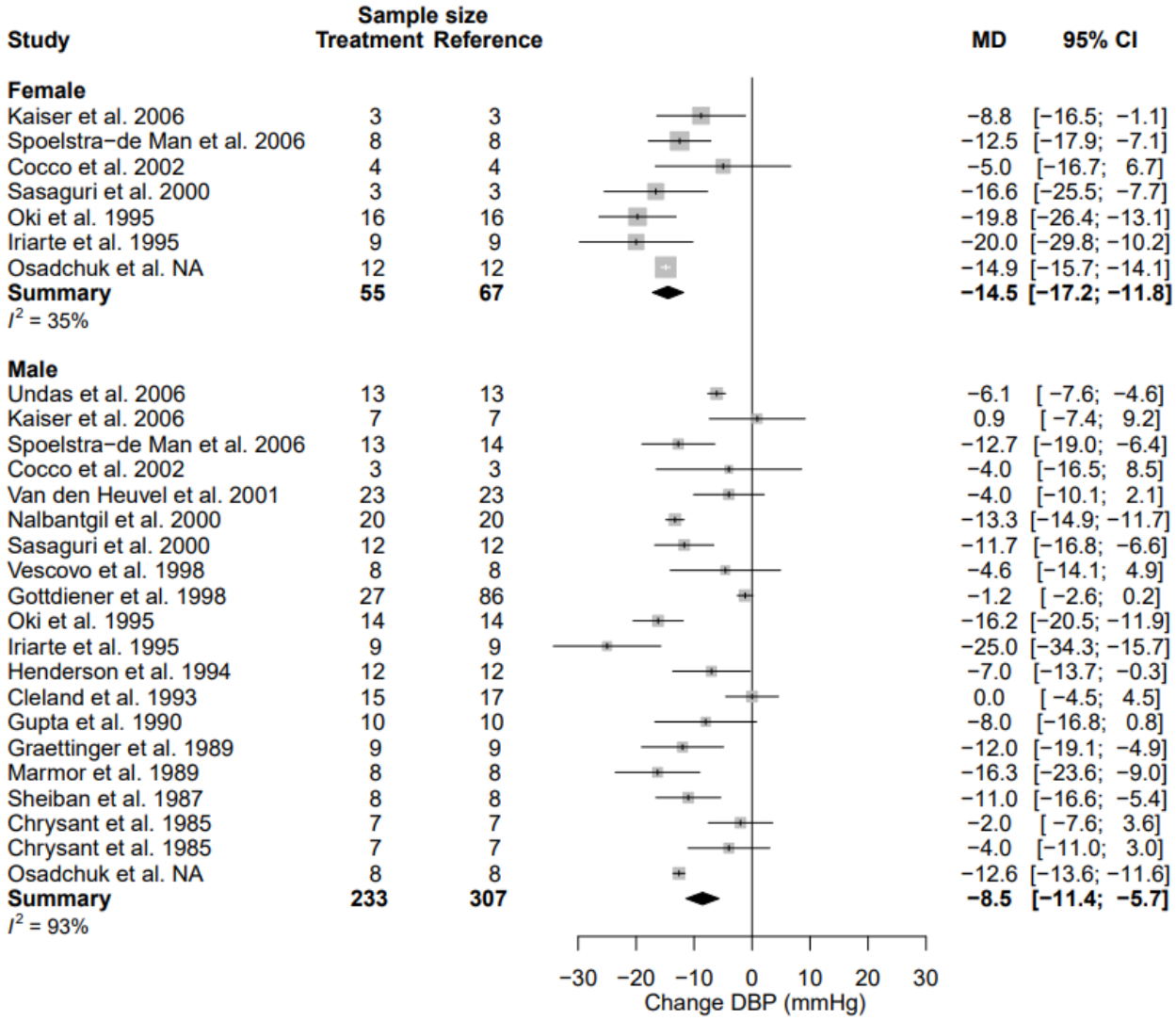

Figure 9 Forest plot of diastolic blood pressure (DBP) change in mmHg after ACEI use compared to baseline for females and males. MD = mean difference

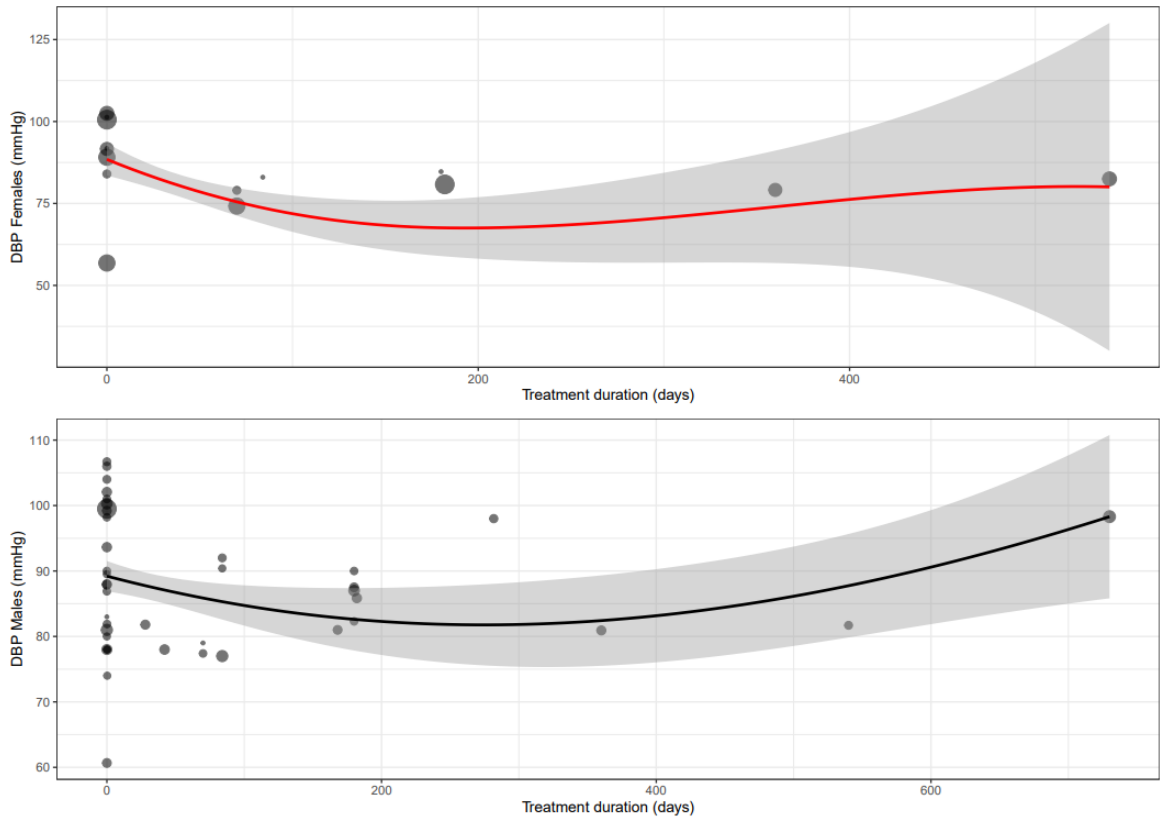

Figure 23 Meta-regression curve of diastolic blood pressure (DBP) by treatment duration (days). Every circle is representing one article and the size represents the amount of participants included in the study, shown as a small or larger circle

HEART RATE:

The mean HR in the studies population was 76.6 ± 6.2 (SD) beats per minute (bpm) in females and 77.6 ± 9.8 (SD) bpm in males (p-value = 0.333). HR after ACEI use decreased modestly but significantly and was also not statistically significant between sexes. In females as compared to males, HR decreased after ACEI use by -3.5 bpm (95% CI, -6.1; -0.9) (-4.8% (95% CI, -8.3; -1.2)) versus -2.5 bpm (95% CI, -4.8; -0.2)(-3.4% (95% CI, -6.2; -0.3)), respectively (p-value = 0.579) (Table 2, Figure S12). Heterogeneity was low in female (I^2 = 39%) and high in male (I^2 = 79%) data.The clinical source of heterogeneity was a difference in antihypertensive compound, ramipril, which significantly affected the magnitude in change in HR in negative trend (Table 3).

The mean difference for HR by treatment duration is reported in Table 4. In both females and males, chronic ACEI treatment effects are comparable (Figures S13, S14). Acute ACEI treatment in females showed no effect. In males, acute, subacute and chronic treatment showed comparable effects.

LEFT VENTRICULAR EJECTION FRACTION:

The mean LVEF in the studies population was 48.2 ± 14.4 (SD) % in females and 44.6 ± 19.4 (SD) % in males (p-value = 0.295). In females, LVEF changed by +2.3% (95% CI, 0.8; 3.7) (5.2% (95% CI, 1.8; 8.6)) as compared to +1.5% (95% CI, 0.6; 2.3) (3.5% (95% CI, 1.5; 5.5)) in males (p-value = 0.340) (Table 2, Figure 15). Heterogeneity was moderate in female (I^2=49%) and low in male (11%) data. The clinical sources of heterogeneity detected

by meta-regression analysis were differences in antihypertensive compound, enalapril, ramipril and perindopril (Table 3).

The mean difference for LVEF by treatment duration is reported in Table 4. Data derived from subgroups showed that the observed subacute increase in LVEF in females is greater than acute and chronic treatment effects. In male data, acute ACEI treatment was responsible for the greatest increase. Acute and chronic treatment effects are comparable between sexes, whereas subacute treatment effects show an opposite LVEF response (Figures S8, 9 and S16).

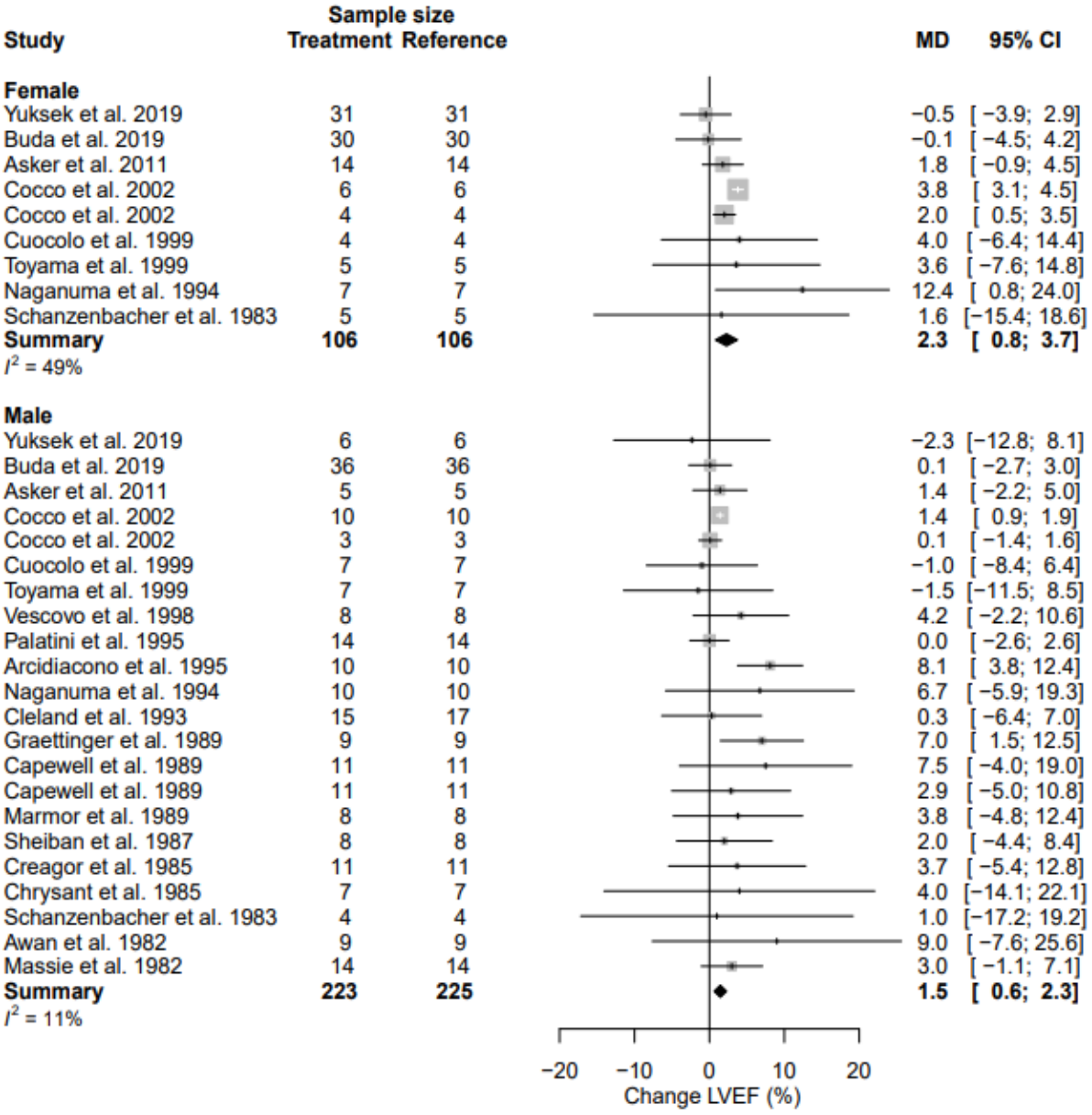

Figure 15 Forest plot of left ventricular ejection fraction (LVEF) change in % after ACEI use compared to baseline for females and males. MD = mean difference

LEFT VENTRICULAR MASS:

For females' only one study measuring LVM was included with a mean of 185.6 ± 45.6 (SD) g (unindexed value). The mean LVM in the studies population was 52.3 ± 11.4 (SD) g in males.

In females, LVM changed by -24.7 g (95% CI, -59.2; 9.7) (-13.3% (95% CI, -31.9; 5.2)) as compared to -3.6 g (95% CI, -30.7; 23.6) (-1.4% (95% CI, -12.3; 9.4)) in males (p-value = 0.344) (Table 2, Figure S18). Neither the change within groups nor the difference between sexes reached statistical significance. Heterogeneity was not measurable in female data due to inclusion of one study and high in male data (I^2=52%). The change in LVM was not significantly affected by clinical and methodological sources of heterogeneity (Table 3).

The mean difference for LVM by treatment duration is reported in Table 4. Chronic ACEI treatment effects showed a greater decrease in females compared to males, however, in both sexes these effects were not significant (Figures S19, S20).

Discussion

In this systematic review and meta-analysis we show that ACEIs lower blood pressure (SBP, DBP) and HR and increase LVEF in females and males, but the drop in DBP is substantially larger in females as compared to males.

One of the key elements of the RAAS is the enzyme ACE, which, by converting angiotensin I to angiotensin II, enables vasoconstriction and increases aldosterone secretion from the adrenal cortex, and with it renal sodium reabsorption and volume retention[69]. Although clinical trials investigating sex differences of drugs targeting the RAAS are scarce, many studies have shown that sex influences the mechanism of action of the RAAS[70]. Females have a lower plasma renin activity than males[71,72]. Besides, ACE-activity has been reported to be higher in postmenopausal compared to premenopausal females. However, a similar level of ACE-activity was reached when postmenopausal females received hormonal substitutive therapy[73-75]. In a cohort of the Framingham Heart study, an insertion/deletion polymorphism analysis revealed an association between a DD genotype and a higher DBP in male, but not in female participants[76].

Sex differences have also been described in the sympathetic nervous system, endothelin-1, the immune system, and sex hormones[75,76]. The immune system plays a role in the low-grade inflammatory state commonly seen in hypertension[77] and sex differences have been described in its causal mechanism, whereby males seem to be more prone to develop hypertension than females[78]. The sex hormone estrogen exerts downregulation of angiotensin II and upregulation of the non-classical RAAS angiotensin-(1-7)-ACE2-MasR/AT2R pathways, and these actions both result in fortified vasodilatory responses. Testosterone, on the other hand, increases the classical angiotensin II driven ACE-Ang II AT1R pathways, causing vasoconstriction, sodium and water retention[76,79,80]. These antagonistic sex hormone induced differences in the RAAS may be responsible for diversities in pathophysiological hypertension etiology and clinical presentation. Sex-specific differences in adrenergic mechanisms have been described in sensitivity of resistance vessels, whereby females react more

extensively to vasodilatory beta-adrenergic stimulation and less extensively to vasoconstrictive norepinephrine mediated effects[81-83]. Endothelin-1, considered the most vigorous endogenous vasoconstrictor, is a sex hormone influenced etiological factor in de development of hypertension. Estrogen and progesterone induce inhibition of endothelin-1, whereas testosterone induces an increase of endothelin-1[84,85].

Although sparsely, there are studies showing sex differences in the effectiveness of ACEIs. While only including 12% of female participants, one study demonstrated that enalapril was effective in reducing congestive heart failure related morbidity and mortality in males, whereas these effects were absent in females[86]. A subsequent study, including less than 20% of female participants, investigated captopril effectiveness on acute myocardial infarction patients and revealed comparable results in favor of the male sex[87]. Conversely, more recent studies did not support these findings and have shown comparable beneficial effects in both sexes in response to ACEIs. Nonetheless, the number of female participants in these studies remained less relative to male participants[88-91]. This female underrepresentation is an important and astonishing finding that we have noticed across included studies. Although not the main aim of our study, this finding deserves awareness. Besides the finding that females are underrepresented in clinical trials regarding ACEIs, sex-stratified effects are also sparsely reported in these studies. Although the amount of female participants in clinical trials regarding antihypertensive has increased between 2011 and 2020, still only one third of the included participants seem to be females[92]. Two recently published systematic reviews and meta-analyses on differences in the sex-stratified effects of calcium channel blockers and beta-blockers also reported on this topic and stressed the need for more sex-stratified data in future clinical trials[93,94].

Although hypertension prevalence increases with age in both sexes, rates are higher in postmenopausal females after the age of 60 compared to age-matched males[95,96]. Decreased estrogen levels in postmenopausal females are thought to be responsible for this finding due to attenuation of its cardiovascular preventive effects. Estrogen plays a key role in hypertension prevention by causing vasorelaxation, inhibiting sympathetic activity, preventing vascular remodeling, and decreasing aortic stiffness via endothelial and vascular smooth muscle cells. Herewith is a postmenopausal state linked to an increased risk of hypertension[97].

While elevated SBP may relate to vascular stiffness, DBP is thought to predominantly reflect vascular impedance. The stronger drop in DBP in female as compared to male suggests a larger fall in total peripheral vascular resistance. On the one hand, lower angiotensin II levels may underlie this loss in resistance. Moreover, this may also subsequently lower aldosterone-related sodium and volume retention. On the other hand, less AT receptor stimulation may also underlie the observed decrease in blood pressure. If so, than ARBs may be equally but sex specifically effective in lower DBP. The prior mentioned differing pathways including the ACE versus ACE2 gene, have been described to possess opposing effects and are suggested to negatively regulate one another. However, the complete in vivo mechanism of

ACE2 and its role in sex differences in response to ACEIs and ARBs remains unclear[98]. A lower RAAS activity in females would suggest an overall lower efficacy of RAAS inhibitors in this sex[99]. Since estrogen downregulates and testosterone upregulates the classical pathway containing ACE, one can suppose that ACEIs may work more efficiently in female compared to male patients, since with the same ACEI dose less ACE needs to be weakened in these females[100-102]. Conversely, estrogen decreases the type 1 angiotensin II receptor density, which causes fewer binding sites for ARBs in female versus male patients. However, most of the available evidence on these subjects is rooted in animal studies, making appropriate clinical sex-specific studies necessary[99]. In addition, given the mean age of studied subjects, estrogen effects are possibly of minor importance in our made observations.

Evident sex-specific treatment recommendations are not given in European and American Guidelines for the management of arterial hypertension, except for pregnancy being a contraindication for ACEIs, ARBs and diuretics[103,104]. In line with this, this review indicates comparable effects in both sexes which would suggest universal treatment to be sufficient. This study supports the hypothesis that both sexes have the same outcome on equivalent doses of ACEIs and raises the question if pharmacodynamic and pharmacokinetic established sex differences actually have a clinically significant impact, at least in primarily post-menopausal female.

Strength and limitations

There are some limitations to mention. First, some included hypertensive patients received imperative co-medication for concurrent underlying disease which could have biased the observed intervention effect. Second, this meta-analysis included more studies with male subjects, which caused female underrepresentation and loss in scientific power regarding treatment effects. Future studies may benefit from balancing the representation of females and males in their studies. Third, the mean age of almost all studies including females is around or above the median expected age of menopause, and, as such, may attenuate possible sex-related differences in blood pressure response as a consequence of loss in cardioprotective effects of estrogen [96,105]. Fourth, our results predominantly apply to postmenopausal females, high blood pressure is most often diagnosed and treated in postmenopausal state making our results clinically relevant.

Conclusion and recommendation

In this systematic review and meta-analysis, ACEIs demonstrated to lower SBP, DBP and HR and increased LVEF significantly in both females as compared to males. Although most included female individuals were past menopause and female participants were underrepresented, sex did only have a significant different effect on DBP.

Declaration of Competing Interest:

All other authors declare no interest. Furthermore, there are no known conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that all have approved the order of authors listed in the manuscript.

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Author's contribution

SL, DM, NW, ZM, EV, EL, MV, SH, CD, MA, JW: performed the search, study selection and data extraction. SL: analyzed the data. SL, DM: wrote the initial draft of the paper, revised the paper and finalized the manuscript. SL, DM: wrote the paper. MS, CG: initiated the project, developed the idea and coordinated the writing process. SL, DM, MS, CH: wrote the paper and critically reviewed the content.

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None

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Appendix

Table 1 Characteristics of studies

Study	Patient	Ethnicity	ACEI treatment (administration)	Mean dose (mg/day)	% max dose*	Subjects ARBs (n)			Control group†	Controls (n)			Age (years + SD)	Intervention duration (days)	Study design	Extracted variables	Mentioned method(s) of measurement
Kaiser[23] (2006)	HTN, DM	-	Enalapril (oral)	10	25	10	7	3	Nebivolol	10	7	3	58.5 (7.0)	84	RCT	MAP, SBP, DBP, HR	Sphygmomanometry
Cocco[24] (2002)	HF	-	Enalapril (oral)	22.5	56.25	7	3	4	Placebo	7	3	4	-	70	RCT	MAP, SBP, DBP, HR, LVEF	ECG, doppler, echo
Burggraaf[25] (1998)	-	-	Captopril (oral)	50	33.3	9	9	0	Nifedipinean d placebo	9	9	0	-	0.125	RCT, crossover	MAP, HR	Sphygmomanometry
Arcidiacono[26] (1995)	HF	-	Captopril (oral)	25	16.7	10	10	0	-	-	-	-	65 (‡)	0.021	Cross-sectional	MAP, HR, LVEF, LVM	Echo
Ahmad[27] (1990)	HF	W, B	Captopril (oral)	13.8	9.2	10	10	0	-	-	-	-	61 (‡)	0.167	Prospective cohort	MAP, HR	SGC, ECG, sphygmomanometry
Capewell[28] (1989)	HF	-	Captopril (oral)	25	16.7	11	11	0	-	-	-	-	64.45 (4.3)	0.0417	Prospective cohort	MAP, HR, LVEF	ECG, sphygmomanometry
Capewell[28] (1989)	HF	-	Captopril (oral)	75	50	11	11	0	-	-	-	-	64.45 (4.3)	90.4	Prospective cohort	MAP, HR, LVEF	ECG, sphygmomanometry
Kramer[29] (1982)	HF	-	Captopril (oral)	300	200	6	6	0	-	-	-	-	60 (‡)	90	Prospective cohort	MAP, HR	Cath
Kramer[29] (1982)	HF	-	Captopril (oral)	182.1	121.4	15	15	0	-	-	-	-	60 (‡)	0.06	Prospective cohort	MAP, HR	Cath
Komajda[30] (1982)	HF	-	Captopril (oral)	182.1	121.4	14	14	0	-	-	-	-	45.6 (14.9)	650	Prospective cohort	MAP, HR	Sphygmomanometry, echo

Brunner[31] (1980)	HTN	-	Captopril (oral)	25	16.7	6	6	0	-	-	-	-		0.3	Prospective cohort	MAP	
Brunner[31] (1980)	HTN	-	Captopril (oral)	25	16.7	8	8	0	-	-	-	-		0.06	Prospective cohort	MAP	
Spoelstra-de Man[32] (2006)	HTN, DM	W	Lisinopril (oral)	15	18.8	22	14	8	Hydrochlorothiazide and candasartan	48	29	19	61.7 (8.3)	360	RCT	SBP, DBP, HR	Sphygmomanometry
Undas[33] (2006)	CAD	-	Quinapril (oral)	10	12.5	13	13	0	-	-	-	-	58.8 (7.3)	28	RCT	SBP, DBP	Sphygmomanometry
Van den Heuvel[34] (2001)	-	-	Enalapril (oral)	20	50	23	23	0	Placebo	20	20	0	62 (9)	84	RCT	SBP, DBP, HR	ECG
Nalbantgil[35] (2000)	HTN	-	Enalapril (oral)	20	50	20	20	0	Valsartan	20	20	0	53.4 (5.5)	180	RCT	SBP, DBP	Sphygmomanometry, echo
Gaudron[36] (2000)	MI	-	Quinapril (oral)	34	42.5	12	12	0	-	-	-	-	66 (6.9)	360	RCT	SBP, HR	Sphygmomanometry
Sasaguri[37] (2000)	HTN, LVH	-	Imidapril (oral)	7.7	77	15	12	3	-	-	-	-	56.8 (11.9)	180	Cross-sectional	SBP, DBP	Sphygmomanometry, echo
Vescovo[38] (1998)	HF	-	Enalapril (oral)	15	37.5	8	8	0	Losartan	8	8	0	59.7 (5.5)	180	RCT	SBP, DBP, LVEF	Sphygmomanometry, echo
Oki[39] (1995)	HTN	-	Enalapril (oral)	8.3	20.8	30	14	16	-	-	-	-	61.6 (7.8)	180	Prospective cohort	SBP, DBP, LVM	Sphygmomanometry, echo
Iriarte[40] (1995)	HTN	-	Enalapril (oral)	15	37.5	11	9	2	-	-	-	-	60.9 (10.))	540	Prospective cohort	SBP, DBP, HR	Sphygmomanometry, echo
Henderson[41] (1994)	HTN	-	Captopril (oral)	56.3	37.5	12	12	0	Placebo	14	14	0	33 (9.2)	28	RCT	SBP, DBP, LVM	Sphygmomanometry, echo

Cleland[42] (1993)	-	-	Lisinopril (oral)	6.3	7.8	18	18	0	Placebo	18	18	0	58 (7)	42	RCT, crossover	SBP, DBP, HR, LVEF	Sphygmo-manometry, echo, doppler
Gupta[43] (1990)	HTN	W	Quinapril (oral)	40	50	10	10	0	Placebo	10	10	0	42 (9.5)	28.2	RCT, crossover	SBP, DBP	Sphygmo-manometry, echo
Marmor[44] (1989)	HTN, LVH	-	Cilazapril (oral)	2.5	25	8	8	0	Placebo	8	8	0	58.5 (7.7)	0.13	RCT, crossover	SBP, DBP, HR, LVEF	Sphygmo-manometry, echo
Graettinger[45] (1989)	HTN	-	Lisinopril (oral)	75	93.8	9	9	0	Atenolol	10	10	0	56 (‡)	84	RCT	SBP, DBP, HR, LVEF, LVM	Sphygmo-manometry, echo
Sheiban[46] (1987)	HTN	-	Captopril (oral)	75	50	8	8	0	Nifedipine	8	8	0	39 (9)	180	Prospecti ve cohort	SBP, DBP, HR, LVEF	Sphygmo-manometry, echo
Chrysant[47] (1985)	HF	-	Enalapril (oral)	10	25	7	7	0	Placebo	7	7	0	62 (10.6)	84	RCT	SBP, DBP, HR	ECG, sphygmo-manometry
Osadchuk[68] (2019)	HTN, CAD	-	Ramipril (oral)	7.9	79	20	8	12	Metoprolol	20	8	12	71.0 (4.6)	70	RCT	SBP, DBP, HR	Sphygmo-manometry, ECG
Buda[49] (2019)	HTN	-	Perindop ril (oral)	7.5	46.9	66	36	30	-	-	-	-	56.3 (10.5)	365	Prospecti ve cohort	HR, LVEF	Echo
Marakas[50] (1995)	-	-	Captopril (oral)	50	33.3	27	24	3	Placebo	10	8	2	57 (9)	0.04	Case-control	HR	ECG
Naganuma[51] (1994)	HF	-	Enalapril (oral)	9.4	23.5	17	11	6	-	-	-	-	53.2 (11.2)	90	Cohort study	HR, LVEF	Echo, radionuclide ventriculograp hy
Schanzenbach er[52] (1983)	HF	-	Captopril (oral)	50	33.3	9	4	5	-	-	-	-	52.1 (9.3)	0.04	Prospecti ve cohort	HR, LVEF	SGC
Wenting[53] (1983)	HF	-	Captopril (oral)	50	33.3	19	14	5	-	-	-	-	58.2 (8.1)	0.06	Cross-sectional	HR	ECG, echo, SGC

Levine[54] (1980)	HF	-	Captopril (oral)	25, 100, 150, 262.5	16.7, 66.7, 100, 175	11	10	1	-	-	-	-	59.1 (8.7)	0.06 - 150	Prospective cohort	HR	SGC
Demirel[55] (2003)	HF	-	Cilazapril (oral)	2.5	25	4	4	0	-	-	-	-	71.5 (4.4)	2555	Retrospective cohort	HR	Echo
Bartels[56] (1999)	CAD	-	Perindoprilat (oral)	0.5	3.1	14	14	0	Placebo	11	11	0	56 (11.2)	0.01	RCT	HR	-
Anand[57] (1990)	HF	-	Enalapril (oral)	10	25	5	5	0	-	-	-	-	-	0.2 and 0.3	Prospective cohort	HR	SGC
Anand[57] (1990)	HF	-	Enalapril (oral)	20	50	3	3	0	-	-	-	-	-	30	Prospective cohort	HR	SGC
Mulligan[58] (1989)	CAD, HF	-	Enalapril (oral)	18.6	46.4	14	14	0	Placebo	14	14	0	50.9 (11.5)	42	RCT, crossover	HR	SGC
Awan[59] (1982)	HF	-	Captopril (oral)	270	180	9	9	0	-	-	-	-	62.8 (12.0)	180	Prospective cohort	HR, LVEF	SGC, echo
Massie[60] (1982)	HF	-	Captopril (oral)	25	16.7	14	14	0	-	-	-	-	60 (‡)	0.06	Prospective cohort	HR	SGC
McGrath[61] (1981)	HF	-	Captopril (oral)	56.3	37.5	9	9	0	-	-	-	-	62.0 (16.0)	7	Prospective cohort	HR	SGC
Yuksek[62] (2019)	HF	-	Perindoprilil (oral)	5	31.3	37	6	31	-	-	-	-	61.7 (7.9)	330	RCT	LVEF	Echo
Asker[63] (2011)	HTN	-	Ramipril (oral)	5	50	20	6	14	-	-	-	-	52.8 (8.9)	180	Prospective cohort	LVEF	Echo

Cuocolo[64] (1999)	HTN	-	Enalapril (oral)	30	75	11	7	4	Valsartan	11	7	4	48 (8)	28	RCT, crossover	LVEF	Sphygmo-manometry, echo
Toyama[65] (1999)	HF	-	Enalapril (oral)	7.5	18.8	12	7	5	Metoprolol	12	7	5	55.7 (13.2)	365	RCT	LVEF	Echo
Palatini[66] (1995)	HTN	-	Quinapril (oral)	20	25	14	14	0	-	-	-	-	26 (7)	90	Prospective cohort	LVEF	Echo
Creagor[67] (1985)	HF	-	Enalapril (oral)	25	62.5	11	11	0	Placebo	12	12	0	53.6 (12.8)	84	RCT	LVEF	Radionuclide ventriculography

* Percentage of maximal dosage for the indication hypertension. Enalapril 40 mg/day orally[106]; captopril 150 mg/day orally[107]; lisinopril 80 mg/day orally[108]; quinalapril 80 mg/day orally[109]; imidapril 20 mg/day orally[110]; cilazapril 10 mg/day orally[111]; ramipril mg/day orally[112], perindopril 16 mg/day[113], perindoprilat 16 mg/day[113] † Control group: other antihypertensive treatment (other than angiotensin-converting-enzyme inhibitors), placebo or non-drug intervention. ‡ SD not reported.

Data presented as mean ± SD or percentages. B = black, CAD = coronary artery disease, cath = catheterization, DBP = diastolic blood pressure, DM = diabetes mellitus, doppler = doppler ultrasonography, echo = echocardiography, ECG = electrocardiography, HR = heart rate, HF = heart failure, HTN = hypertension, LVM = left ventricular mass, LVEF = left ventricular ejection fraction, LVH = left ventricular hypertrophy, MAP = mean arterial pressure, MI = myocardial infarction, RCT = randomized controlled trial, SBP = systolic blood pressure, SD = standard deviation, SGC = Swan-Ganz catheter, W = white.