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REVIEW ARTICLE

Sex Differences in the Efficacy of Angiotensin Receptor Blockers in Blood Pressure Lowering and Cardiac Remodeling: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Hypertension is the leading risk factor for cardiovascular disease (CVD) in females. While treatment of high BP is essential in the global prevention strategies of CVD it is assumed that effectiveness of pharmacological treatment may be different across sexes.

Objective: The aim of this systematic review and meta-analysis was to evaluate sex-stratified effects for angiotensin receptor blockers (ARBs) on blood pressure (BP), heart rate and cardiac function in female compared to male hypertensive individuals.

Design and methods: We performed a series of systematic reviews and meta-analysis after we systematically searched PubMed and EMBASE for studies evaluating the effects of the five major groups of antihypertensive medication from 1945 to May 2020. We included randomized control trials and observational studies in humans (≥18 years) investigating Beta-blockers (BB), angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), and diuretics. In this study we analysed data on ARB's. Studies had to present both baseline and follow-up measurements of at least one of the outcome variables of interest and present their data in a sex-stratified manner. Data on BP, heart rate and cardiac function were retrieved from studies. Mean differences between baseline and follow-up were calculated using a random-effects model. Intervention effect was assessed for the acute (0-14 days), subacute (15-30 days) and chronic (>31 days) phase.

Results: The search strategy resulted in 73,867 hits. After first screening based on title and abstract, 15,130 articles were suitable for full text screening. After excluding all studies that matched our exclusion criteria, 205 studies were eligible for analysis for the five antihypertensive drugs. Studies investigating ARB´s (n=17) were used in this review. ARB decreased BP significantly but comparably in both female and male; systolic BP -18.2 mmHg (95% CI, -24.8; -11.5) vs -20.1 mmHg (95% CI, -26.7; -13.6) and diastolic BP -11.6 mmHg (95% CI, -14.7; -8.4) vs -12.3 mmHg (95% CI, -16.4; -8.1). Left ventricular ejection fraction (LVEF) did not change significantly in either group. Left ventricle (LV) mass was only reported in males and did not change statistically significant -11.8 g (95% CI, -25.6; 1.9).

Conclusion: ARB's decreased BP in both female and male hypertensive patients substantially but comparably.

Keywords: hypertension; angiotensin receptor blockers; sex differences

Introduction

Cardiovascular diseases (CVD) are the leading cause of death in females worldwide and responsible 35% of all female deaths in 2019 [1] [2] [3 4]. Hypertension is the leading risk factor for CVD morbidity and mortality and is considered the most substantial health burden in female [5]. Timely reduction of BP has proven to prevent the development of CVD later in life [6] and antihypertensive medication is the most effective therapy to decrease BP [7]. There are differences in female compared to male in system-biology, clinical manifestations, treatment effects and outcomes of CVD [8 9]. As the effects of antihypertensive treatment are predominantly studied in male, the contemporary sex-neutral treatment recommendations may therefore result in attenuated tolerance of instituted medication, suboptimal preventive care, and with it, possible avoidable hypertension-related cardiovascular events, which may contribute to less favorable outcomes in female [10] [11].

One of the first-line antihypertensive treatment options in current guidelines are angiotensin receptor blockers (ARBs) which exert their effects as selective ligands of the angiotensin II receptor type 1, subsequently blocking the circulatory effects of angiotensin II [12]. Clinical trials on ARBs showed appropriate BP control [13].

There are sex specific differences in the pharmacokinetics of ARBs in female compared to male, that have been linked to estrogen affecting the renin-angiotensin system (RAS) [14]. To date, almost none of these trials have explicitly investigated the treatment effects sex-specifically. It can be therefore questioned whether ARBs are equally effective in both sexes. To this end, we studied in a systematic review and meta-analysis the intervention effects of ARB treatment on cardiovascular and hemodynamic variables in female versus male adults.

Methods

SERIES OF META-ANALYSIS

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

LITERATURE SEARCH

An extensive systematic literature search was conducted on articles evaluating the effects of antihypertensive medication on cardiovascular and hemodynamic variables using PubMed (NCBI) and Embase (Ovid) databases. PubMed and Embase provided publications published from 1945 to May 2020 respectively, the search terms are presented in Table S1. The search strategy aimed at studying the effect of the five antihypertensive drugs on BP, left ventricular geometry and left ventricular function (BB), angiotensin converting enzyme inhibitors (ACE-I), ARB, calcium channel blockers (CCB), and (DIU). The search limits used were 'humans' and 'journal article'. The search served to study the following objective:

1. To study differences and similarities between female and male in the effect of antihypertensive medication on BP, cardiac function and geometry.
2. The data for each antihypertensive drug were analyzed separately for five different antihypertensive compounds. The objective of the current manuscript was to study differences and similarities between female and male in the effect of ARBs on BP, cardiac function and geometry.

ELIGIBILITY CRITERIA

The identified articles were assessed for eligibility in two phases (Figure 1). First, all studies were independently screened for eligibility based on the title and abstract by independent duos of ten investigators. Second, articles were screened based on full text suitability based on the inclusion and exclusion criteria also by independent duos of the same ten investigators. Discrepancies for first and second selection were resolved by mutual agreement of two investigators.

Studies were only included if they 1) investigated one class of the five main groups of antihypertensives (BB, ACE-I, ARB, CCB, and DIU), 2) were human studies, 3) included adults >18 years of age, 4) were written in English or Dutch, 5) had a suitable study design (randomized controlled trials (RCTs), prospective and retrospective cohort studies).

We excluded articles if 1) only the abstract was available and full report was not found, 2) they had an unsuitable study design (systematic reviews and meta-analysis, literature reviews, case reports, animal studies, and in vitro studies), 3) no original data were included, 4) no antihypertensive medication was used, 5) more than one antihypertensive medication was used simultaneously, 6) data were not reported

separately for females and males, 7) no reference group was included (control, placebo, other antihypertensive medication group), 8) the outcome was not related to one of the predefined variables (systolic and diastolic BP, heart rate, cardiac output, left ventricular ejection fraction, left ventricular mass and/or EA ratio), 9) data was not reported as standard deviation (SD), standard error (SE), or 95% confidence interval (95% CI), 10) there was no registration of specific dose and duration, 11) participants were undergoing invasive operations, performing exercise during measurements, or undergoing dialysis or chemotherapy.

If articles presented their data differently (for example, median with interquartile range), mean values with SD were requested from the authors by email.

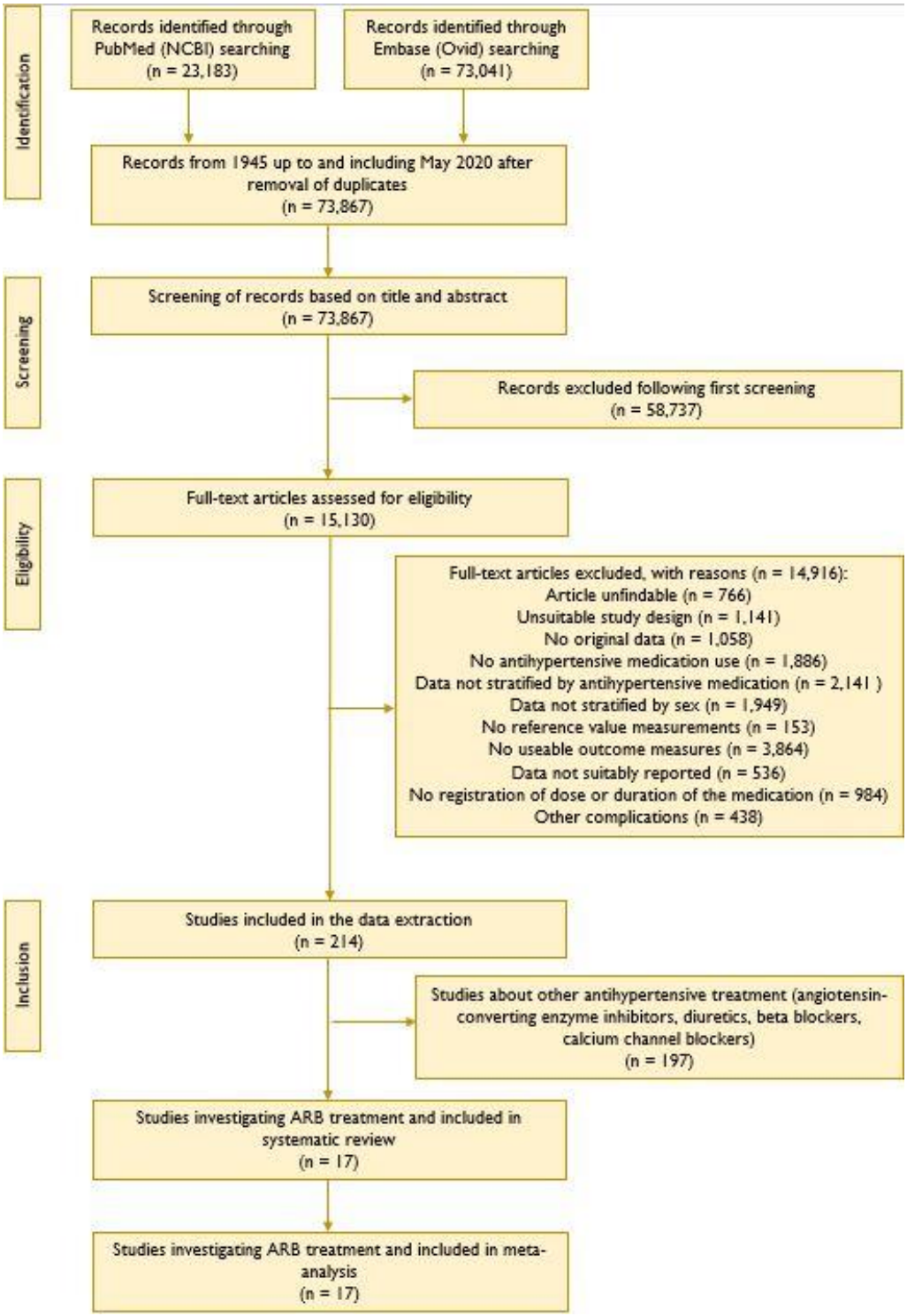

Figure 1 Flowchart of study selection and inclusion after systematic literature search.

STUDY SELECTION

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 approached by e-mail or via research gate to request sex-specific data, and received a reminder after two weeks. 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 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.

DATA EXTRACTION

Studies had to focus on acute (0-14 days) , subacute (15-30 days) and/or chronic (>31 days) therapy. 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 ARB intervention of systolic and diastolic an mean arterial BP, heart rate, cardiac output, left ventricular ejection fraction, and left ventricular mass) were collected in a predesigned format. 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. Baseline and post-intervention mean including SD for the outcome variables.

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 receive this judgement. To receive an overall judgement of “High risk of bias”, at least one of the domains was scored 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 and differences were solved by a third independent reviewer.

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 Der Simonian 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 (20). 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 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 [19]. Sources of clinical heterogeneity (ARB 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 [20 21].

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 this full text assessed studies, 14,916 (98.6%) matched at least one exclusion criterion. 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 criterion 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 were 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.

Eventually, a total of 214 articles were included for the whole series of which 17 articles reported on ARBs and were included in this study [22-38] (Table 1, appendix).

STUDY CHARACTERISTICS

Study characteristics and anthropometric data are visualized in Table 1 (appendix). Data of 15,570 subjects using ARBs were included in this meta-analysis, of whom 6,845 (44%) were female. The mean age of the subjects from the included studies was 65.1 ± 11.8 (SD) years.

Six studies analyzed the effects of losartan [22 24 31 35 37 38], four of valsartan [25 29 30 32], two of candesartan [26 34], four studies irbesartan [28], fimasartan [33], telmisartan [23] and eprosartan [36], respectively. One study reported on both fimasartan and losartan [27]. The percentage of the maximum dose of ARBs given was 57.2 ± 0.28 (SD) % for females and 56.0 ±0.25 (SD) % for males.

Mean arterial BP was studied in two studies [28 29], systolic BP in 15 studies [22-24 26-36 38], diastolic BP in 14 studies [22-24 26-35 38], heart rate in six studies [27-29 33 34 38], left ventricular ejection fraction in four studies [25 27 28 35] and left ventricular mass in two studies [37 38].

One study measured acute as well as chronic effects of the administered ARB [30]. Two included studies evaluated the subacute effects of ARBs [23 25]. All of the included studies measured the chronic effects of ARB treatment, which means a follow-up period of 31 days or longer.

Study designs consisted of 15 randomized controlled trials [22 23 25-30 32 34-38] of which one was a crossover study [25] and one a prospective cohort study [37]. Of the other two studies, one was a prospective cohort study [33] and one a case control study [24].

Of the included articles containing ARB interventions, five studies included only male subjects [24 32 35 37 38], none included only female subjects and the remaining 12 studies contained subjects of both sexes [22 23 25-31 33 34 36]. Only two out of the 12 studies presented the data stratified for sex [30 33] and 10 studies did not report the outcomes separated for sex [22 24-26 28 29 31 32 34 35 37 38]. Sex-specific data were therefore requested via email.

Publication bias assessed via Eggers's regression showed no significant bias for all of the variables included (Table S2).

QUALITY ASSESSMENT

The quality assessment per domain according the RoB2 tool is summarized in Supplemental Figure 2. Seven out of 17 studies had a low overall risk of bias [25 27-29 31 32 34]. Eight studies had a high overall risk of bias [22-24 30 33 35 36 38]. The prospective cohort study [33] and case control study [24] had both a high risk of bias due to lacking randomization an blinding. The remaining two studies were scored as having some concerns [26 37].

MEAN ARTERIAL PRESSURE

The mean arterial pressure (MAP) in the studies population was 117.6 mmHg in females and 118.6 mmHg in males (p-value = 0.672). The mean difference and relative percentual change from baseline for MAP are reported in Table 2 and Figure 3. In females as compared to males, MAP decreased -14.5 mmHg (95% CI, -21.7; -7.4)) (-12.5% (95% CI, -18.7; -6.4)) versus -17.3 mmHg (95% CI, -29.4; -5.1) (-14.6% (95% CI, -24.9.; -4.3)) (p-value = 0.703), respectively. Heterogeneity was high in both female (I^2 = 80%) and male (I^2 = 96%) data. Heterogeneity in MAP response was significantly affected by the ARB valsartan, treatment duration and dosage (all delineated as clinical sources of heterogeneity) (Table 3).

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

Parameter		Females	Males
MAP (mmHg)	MD	-14.5 (-21.7; -7.4)	-17.3 (-29.4; -5.1)
	%	-12.5 (-18.7; -6.4)	-14.6 (-24.9.; -4.3)
SBP (mmHg)	MD	-18.2 (-24.8; -11.5)	-20.1 (-26.7; -13.6)
	%	-12 (-16.3; -7.6)	-13.1 (-17.3; -8.8)
DBP (mmHg)	MD	-11.6 (-14.7; -8.4)	-12.3 (-16.4; -8.1)
	%	-12.6 (-16.1; -9.2)	-13.0 (-17.4; -8.6)
HR (bpm)	MD	-1.5 (-2.6; -0.3)	-1.4 (-2.8; -0.1)
	%	-2.1 (-3.6; -0.5)	-2.0 (-3.8; -0.1)
LVEF (%)	MD	1.6 (-1.7; 4.9)	0.9 (-1.3; 3.0)
	%	2.5 (-2.6; 7.5)	1.5 (-2.3; 5.3)
LVM (g)	MD	-	-11.8 (-25.6; 1.9)
	%	-	-5.5 (-12; 0.9)

Values are reported as mean difference (MD) and relative change (%) compared to baseline with 95% CI. MAP = mean arterial pressure, SBP = systolic BP, DBP = diastolic BP, 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
Eprosartan	-	0.7433	-	-	-
Fimasartan	-	0.0012	0.0024	0.2192	-
Irbesartan	-	0.0494	<.0001	0.8742	-
Losartan	-	0.0005	0.0002	0.3791	0.9309
Telmisartan	-	<.0001	<.0001	-	-
Valsartan	<.0001	<.0001	<.0001	0.5593	0.9978
Low quality	*	0.3929	0.9787	<.0001	0.1116
Moderate quality	*	<.0001	<.0001	-	-
Treatment duration	<.0001	0.1333	0.0370	0.0042	0.3638
% max dose	<.0001	0.3786	0.0416	0.0119	0.1154

*Quality is not included because there are only low quality studies.

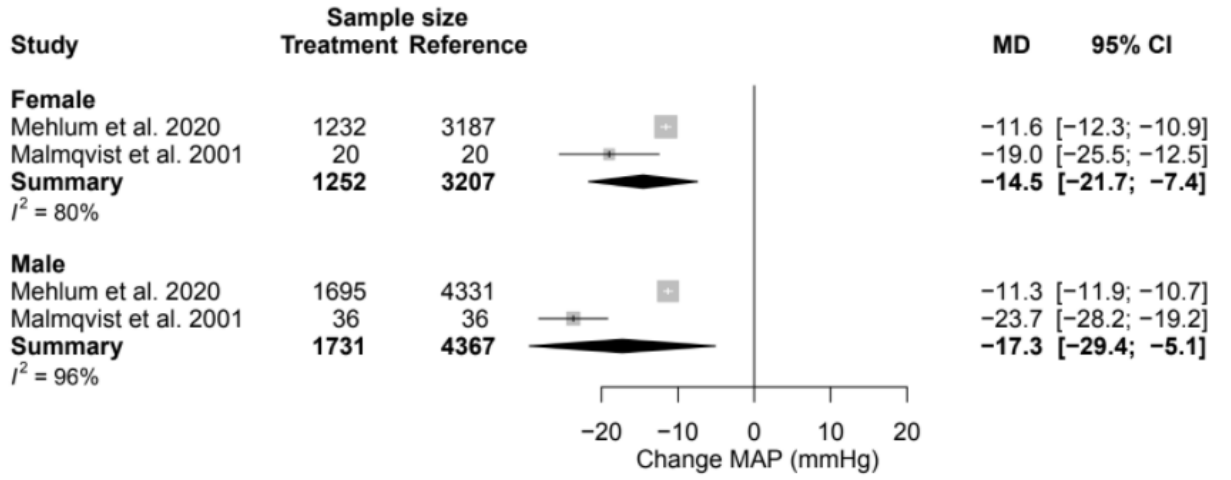

Figure 3 Forest plot of mean arterial pressure (MAP) change in mmHg after ARB use compared to baseline for females and males. MD = mean difference

SYSTOLIC BLOOD PRESSURE

The mean SBP in the studies population was 151.4 mmHg in females and 153.8 mmHg in males (p-value = 0.284). SBP decreased significantly by -18.2 mmHg (95% CI, -24.8; -11.5) (-12% (95% CI, -16.3; -7.6)) in females as compared to -20.1 mmHg (95% CI, -26.7; -13.6)) (-13.1% (95% CI, -17.3; -8.8)) in males (Table 2, Figure 4). This change was not statistically significant between sexes (p-value = 0.679). Heterogeneity was high in both female (I^2 = 99%) and male (I^2 = 99%) data. The clinical sources of heterogeneity detected by meta-regression analysis were differences in antihypertensive compound, fimasartan, irbesartan, losartan, telmisartan and valsartan (Table 3). The moderate study quality, 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, acute and subacute treatment effects on systolic BP were the greatest as compared to chronic ARB treatment (Supplemental Figures 5, 6), an observation also in line with the calculated effect in time by meta-regression analysis (Figure 15).

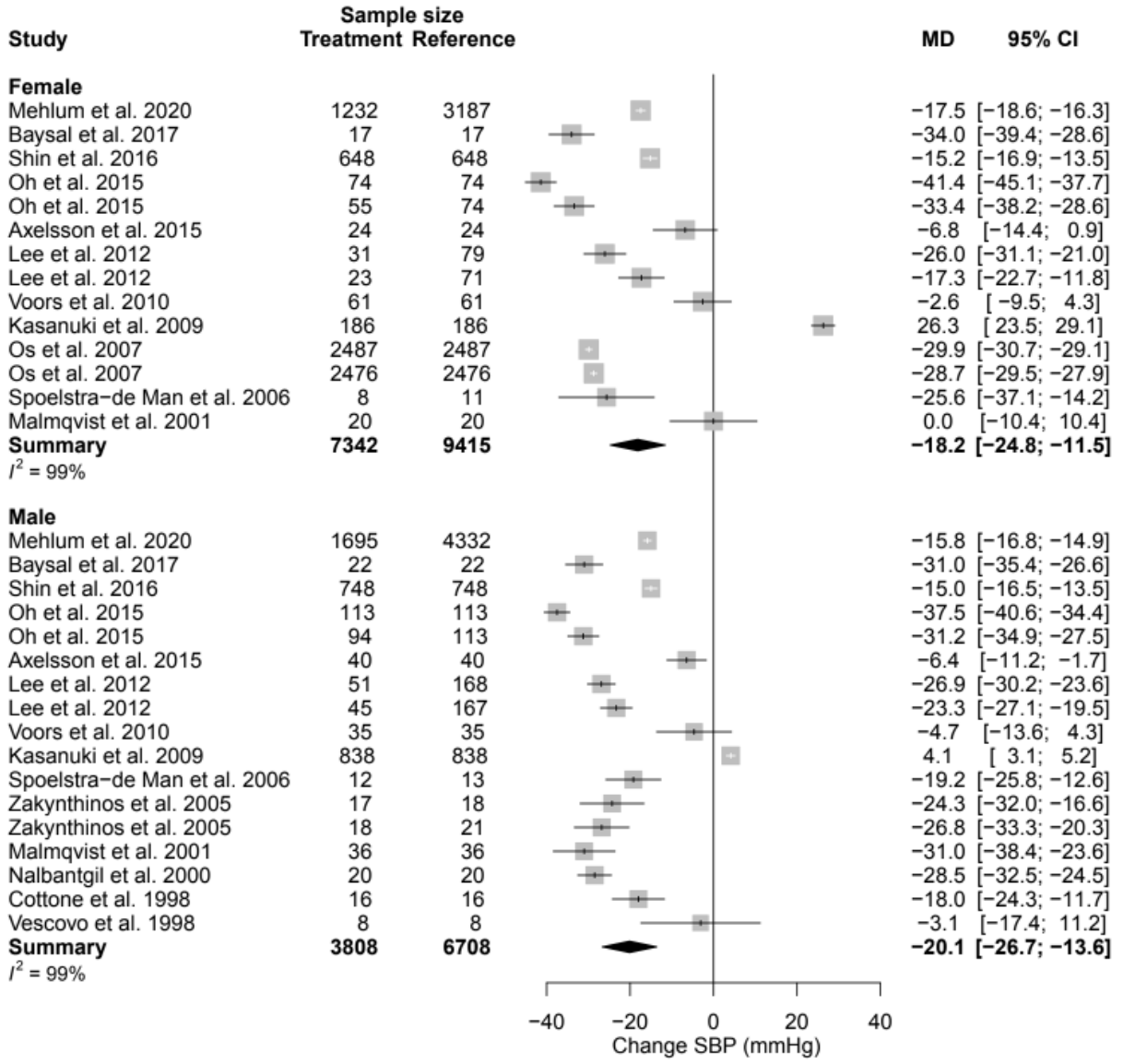

Figure 4 Forest plot of systolic BP (SBP) change in mmHg after ARB use compared to baseline for females and males. MD = mean difference

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

Parameter		Females	Males
SBP (mmHg)	MD acute	-41.4 (-45.1; -37.7)	-37.5 (-40.6; -34.4)
	MD subacute	-34 (-39.4; -28.6)	-31.0 (-35.4; -26.6)
	MD chronic	-14.8 (-22 -7.7)	-18.2 (-24.7; -11.7)
DBP (mmHg)	MD acute	-19.5 (-22.3; -16.7)	-19.1 (-21.5; -16.7)
	MD subacute	-20 (-25.1; -14.9)	-18 (-22.3; -13.7)
	MD chronic	-10.01 (-13.5; -6.7)	-11.3 (-15.7; -7.0)
LVEF (%)	MD acute	4.0 (-7.1; 15.1)	0.0 (-7.4; 7.4)
	MD subacute	1.4 (-2.1; 4.8)	1.2 (-1.6; 4.1)
	MD chronic		

Values are reported as mean difference (MD) compared to baseline with 95% CI. Acute = 0-14 days, subacute = 15-30 days, chronic = >31 days, SBP = systolic BP, DBP = diastolic BP, LVEF = left ventricular ejection fraction.

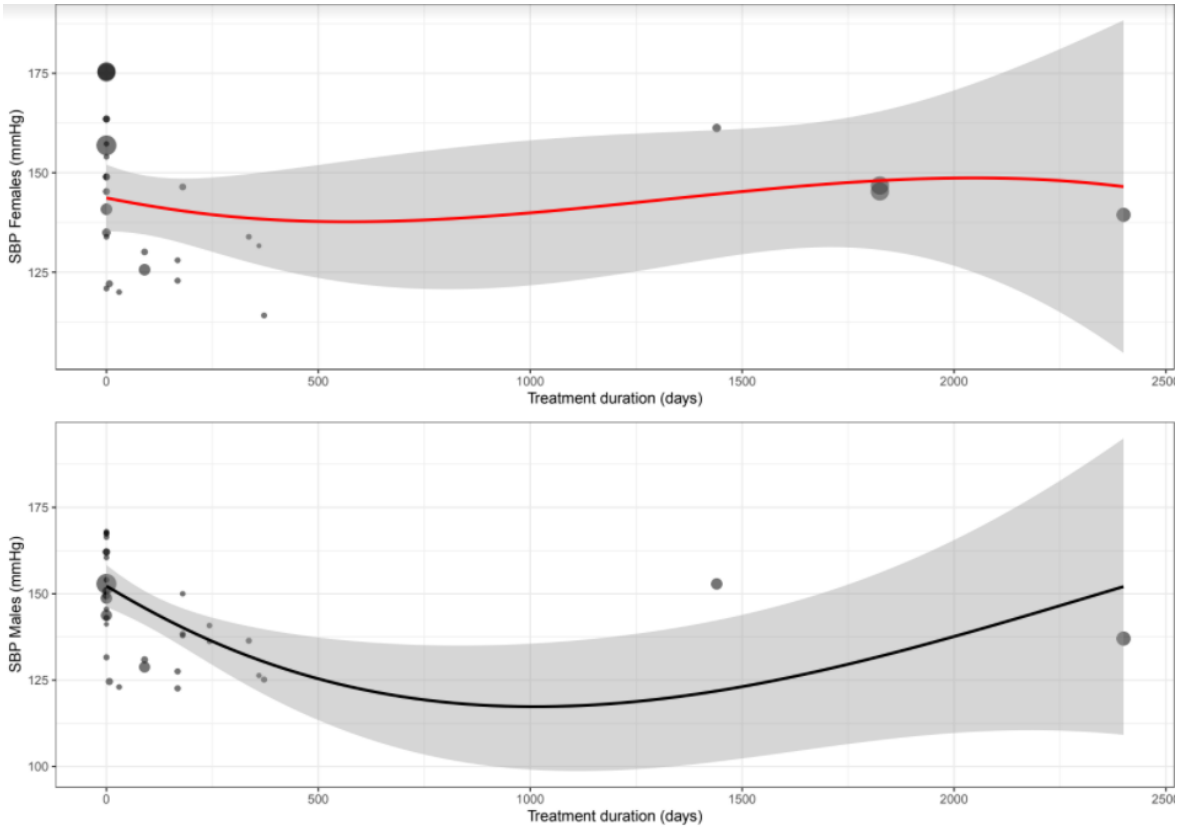

Figure 15 Meta-regression curve of systolic BP (SBP) by treatment duration (days). Every circle is representing one article and the size represents the amount of participants included in the study, shown as a small or larger circle.

DIASTOLIC BLOOD PRESSURE

The mean diastolic blood pressure (DBP) in the studies population was 91.0 mmHg in females and 92.7 mmHg in males (p-value = 0.460). DBP decreased significantly by -11.6 mmHg (95% CI, -14.7; -8.4) (-12.6% (95% CI, -16.1; -9.2) in females as compared to -12.3 mmHg (95% CI, -16.4; -8.1) (-13.0% (95% CI, -17.4; -8.6)) in males (Table 2, Figure 7). This change was not statistically significant between sexes (p-value = 0.790). Heterogeneity was high in both female (I^2 = 99%) and male (I^2 = 99%) data. The clinical sources of heterogeneity were differences in antihypertensive compound, fimasartan, irbesartan, losartan, telmisartan and valsartan, treatment duration and dosage (Table 3). The moderate study quality did

significantly affect the observed change in SBP (Table 3).

The mean difference for DBP by treatment duration is reported in Table 4. Both data derived from subgroups as well as meta regression showed that the observed acute and subacute decrease in DBP is greater in both sexes as compared to chronic ARB treatment (Supplemental Figures 8, 9 and Figure 16).

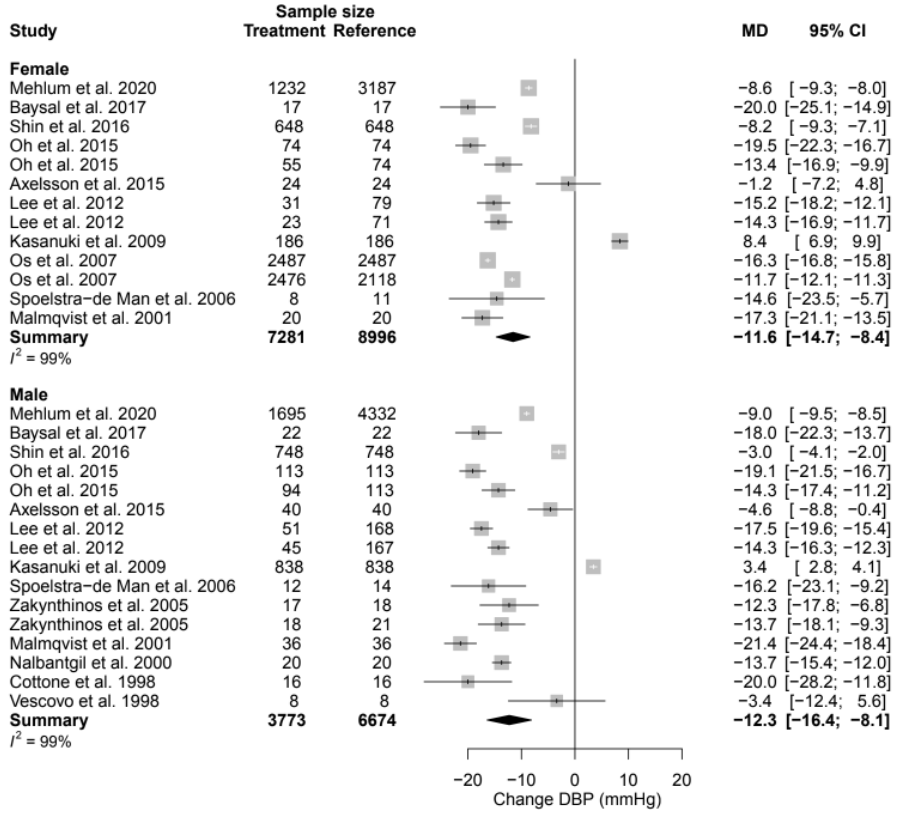

Figure 7 Forest plot of diastolic BP (DBP) change in mmHg after ARB use compared to baseline for females and males. MD = mean difference

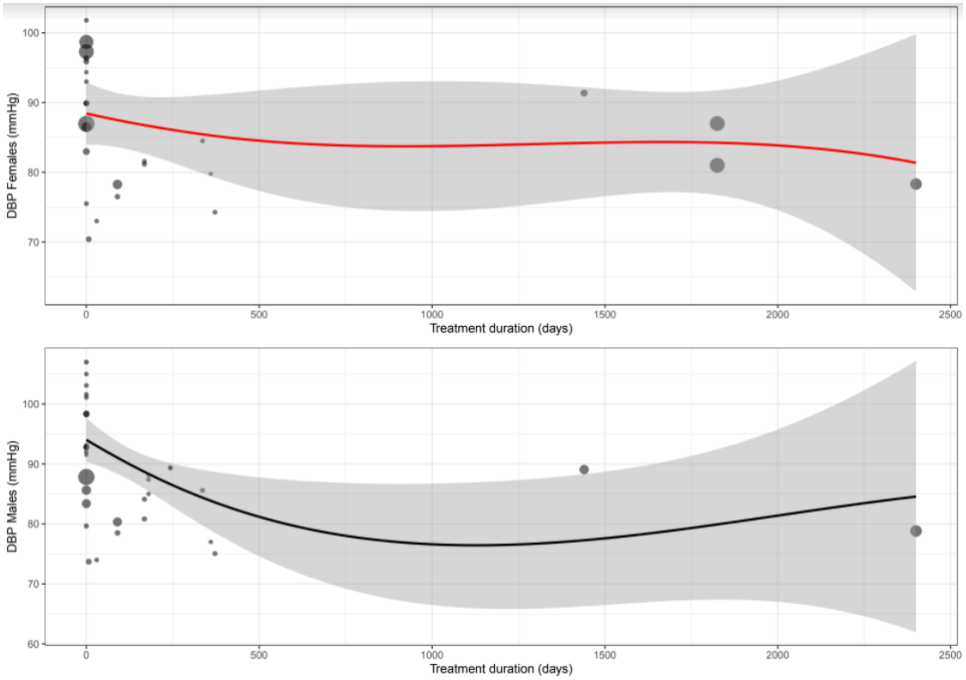

Figure 16 Meta-regression curve of diastolic BP (DBP) by treatment duration (days). Every circle is representing one article and the size represents the amount of participants included in the study, shown as a small or larger circle.

HEART RATE

The mean heart rate (HR) in the studies population was 72.9 bpm in females and 73.1 bpm in males (p-value = 0.820). HR after ARB use decreased modestly but significantly and was also not statistically significant between sexes. In females as compared to males, HR decreased after ARB use by -1.5 bpm (95% CI, -2.6; -0.3) (-2.1% (95% CI, -3.6; -0.5)) versus -1.4 bpm (95% CI, -2.8; -0.1)(-2.0% (95% CI, -3.8; -0.1)), respectively (p-value = 0.942) (Table 2, Figure 10). Heterogeneity was low to moderate in female (I^2 = 45%) and moderate to high in male (I^2 = 71%) data. The clinical sources of heterogeneity, dosage and treatment duration and study quality all significantly affected the magnitude in change in HR (Table 3).

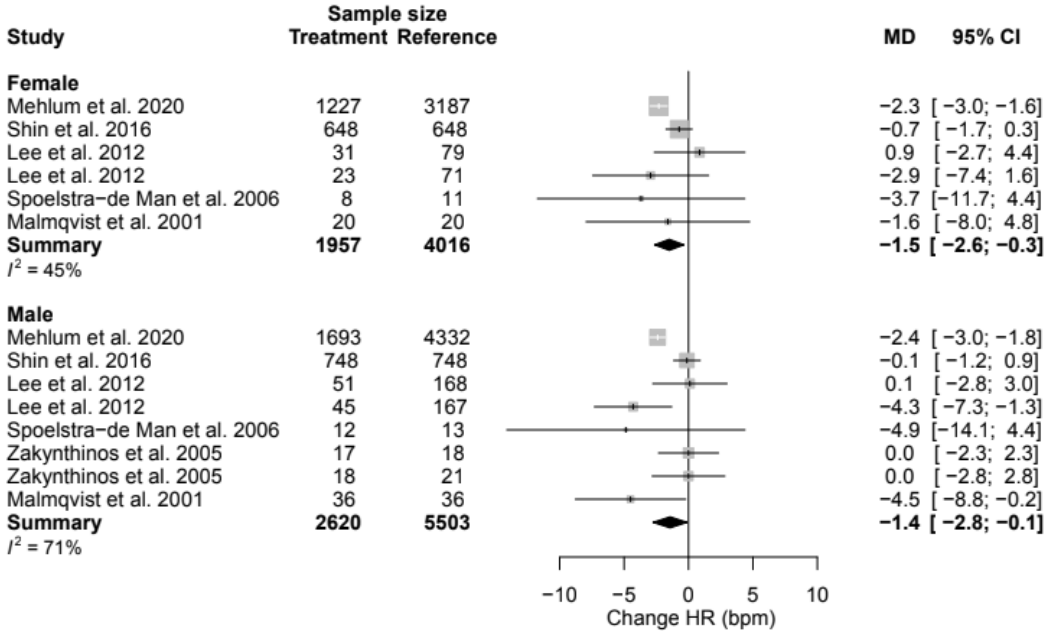

Figure 10 Forest plot of heart rate (HR) change in bpm after ARB use compared to baseline for females and males. MD = mean difference

Left ventricular ejection fraction

The mean LVEF in the studies population was comparable between females and males (63.5% vs 59.5% respectively (p-value = 0.7145)). LVEF did not change significantly in females +1.6% (95% CI, -1.7; 4.9) (2.4% (95% CI, -2.6; 7.5)) and males 0.9% (95% CI, -1.3; 3.0) (1.5% (95% CI, -2.3; 5.3))(Table 2, 11). Neither the change within groups nor the difference between sexes reached statistical significance. Heterogeneity was absent in both sexes (I^2=0%). The change in LVEF was not significantly affected by clinical and methodological sources of heterogeneity (Table 3). Treatment duration did not contribute to differences in reached effect in both sexes (Table 4). (Supplemental Figures 12 and 13).

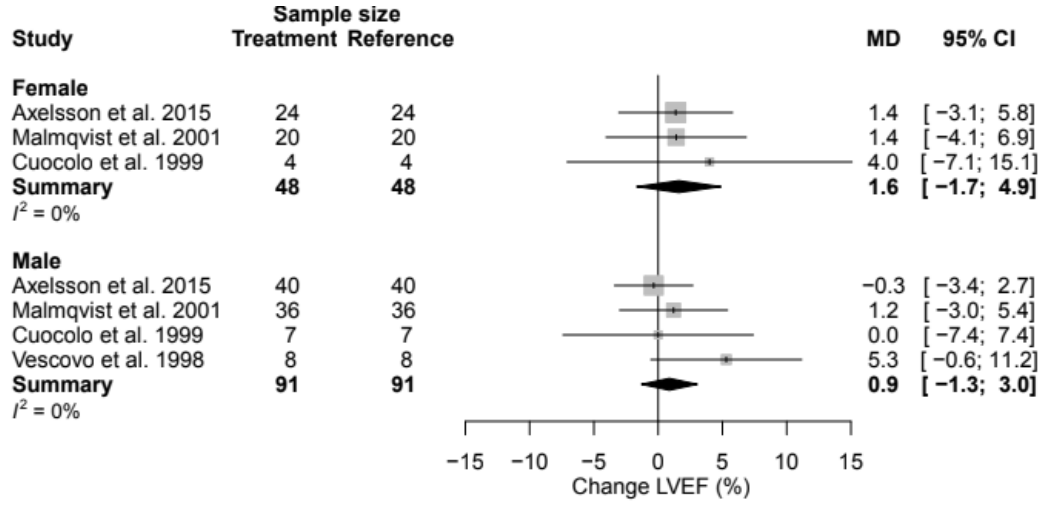

Figure 11 Forest plot of left ventricular ejection fraction (LVEF) change in % after ARB use compared to baseline for females and males. MD = mean difference

LEFT VENTRICULAR MASS

The mean left ventricular mass (LVM) in the studies population was 218 g in males. LVM was examined in two studies and included patients with hypertension and left ventricular hypertrophy, of which one study [38] reported a significant decrease of the LVM index by 12% [37 38]. The change in LVM could only be extracted in males. In these studies, LVM changed by -11.8 g (95% CI, -25.6; 1.9) (-5.5% (95% CI, -12.0; 0.9)) (Table 2, Figure 14), an effect that did not reach statistical significance. Heterogeneity was low in these studies ($I^2 = 7\%$).

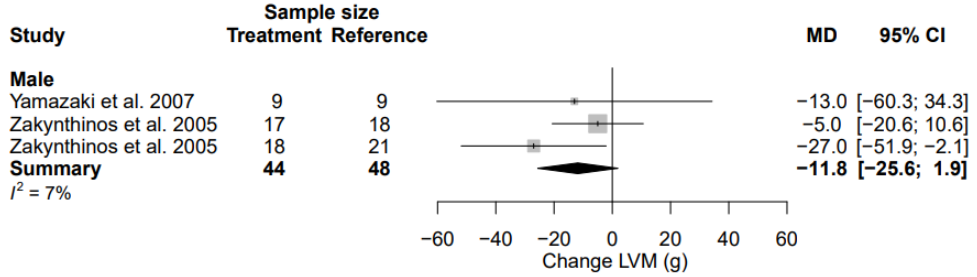

Figure 14 Forest plot of left ventricular mass (LVM) change in grams after ARB use compared to baseline for males. MD = mean difference

Discussion

In this systematic review and meta-analysis, is shown that ARBs lower BP significantly but similarly in both females and males. Only 12 studies were suitable to be used to stratify data based on sex. Markedly, most of the studies did not report primarily their data stratified on sex, but sent it later to us after request.

High BP is the most important attributable but also modifiable risk factor contributing to the global burden of cardiovascular death [39]. ARBs are amongst the first line antihypertensives, but sex differences may affect the effectiveness of BP control and with it adverse remote health and death [9] [40 41] [11 42] [14].

Although this systematic review and meta-analysis showed significant but comparable effects of ARBs in both sexes, sex-specific differences in pharmacokinetic and pharmacodynamic mechanisms among ARB use have been described [43-45]. Sex differences in most important BP regulatory systems have been reported involving amongst the renin-angiotensin system (RAS), the sympathetic nervous system, endothelin-1 (ET-1), the immune system and sex hormones [44 46 47]. Hypertension is usually accompanied by a state of low-grade inflammation in which the immune system plays an essential role [48]. Various studies showed that sex differences exist in the role of the immune system and the development of hypertension, whereby males have been shown to be more susceptible to hypertension than females. Key immunological variables underlying these sex differences are, among others, the ratio of regulatory T-cells to T-helper cells, their corresponding infiltration rates and expression of reactive oxygen species [49].

As ARB induce their effect within the RAS system, we expected to find differences in its BP response. The lack of difference may be a reflection of a truly similar effect, but the heterogeneity of studies and limited number may affect the accuracy of the finding. In addition, in female, high BP is often detected and treated in postmenopausal state (mean age of the subjects in our study was 65.1 ± 11.8 (SD) years) which may reveal potential differences when treated younger female in fertile state. Studies reporting differences in treatment and adverse effects between female and male are sparsely. A systematic review which summarized available evidence on sex differences in adverse drug reactions to heart failure medication, found no sex differences in adverse drug reactions for ARBs. However, this finding referred to only 7% of included data, as these were stratified for sex [50]. As we observed comparable used dosages and were able to quantify variables introducing heterogeneity, we think that our observation supporting comparable BP modulating effects between sexes are valid.

SEX DIFFERENCES IN RAS SYSTEM

The classic RAS is activated when renin cleaves angiotensin to produce angiotensin I, after which angiotensin-converting enzyme (ACE) processes it to form angiotensin II, which thereafter binds the type 1 angiotensin II receptor (AT_1R) [51]. On the one hand, the classic RAS is currently defined as the ACE-Ang II AT1R axis that, when activated, promotes systemic vasoconstriction, sodium and water retention. It has also non-BP related effects including inflammation, oxidative stress, cellular

growth and fibrosis. On the other hand, the non-classical RAS system is activated when angiotensin I is cleaved by ACE2 and neprilysin and subsequently produces angiotensin 1-9 and angiotensin 1-7, respectively. Besides, angiotensin 1-7 can be produced from cleavage of angiotensin II by ACE2 [51]. The non-classical RAS composed primarily of the angiotensin-(1-7)-ACE2-MasR/AT2R pathways generally opposes the actions of the classical stimulated Ang II-AT1R axis by increasing nitric oxide and prostaglandins, mediating vasodilation, natriuresis, diuresis, and lowering oxidative stress. Estrogen mediates vasodilatory downregulation of angiotensin II and upregulation of angiotensin-(1-7)-ACE2-MasR/ AT2R pathways, whereas testosterone increases the vasoconstrictive classical pathways [52-55]. On one hand, these opposing sex-hormone induced properties on the RAS may cause differences in clinical presentation and underlying system-biology towards hypertension between female and male. On the other hand, as non-classical RAS components are thought to contribute to the therapeutic blockade of the classical system to reduce BP, the contribution of the therapeutic effect of ARBs on BP secondary cardiovascular and renal injury may also be different between sexes. As we primarily have looked to BP responses, it may well be that we have missed possible divergent effects within the inflammatory and cellular growth pathways.

SEX DIFFERENCES IN ADRENERGIC MECHANISMS

Vascular tone is predominantly regulated by the sympathetic nervous system, with norepinephrine being the major transmitter targeting alpha- and beta-adrenergic receptors that respectively mediate vasoconstriction and vasodilatation [56 57]. Considerable amount of studies have demonstrated that sensitivity of resistance vessels to adrenergic stimulation is sex-specific [58] by showing that female react more extensively to beta-adrenergic stimulation [59] and create less vasoconstriction to norepinephrine than male [60 61]. These findings are substantiated by the evidence of estrogen receptors that are expressed on endothelial and vascular smooth muscle cells attenuating vascular reactivity to adrenergic stimulation [58]. This sex-specific effect also has an influence on macrovascular level, but here it explains sex differences to a lesser extent [62]. ET-1, the most potent endogenous vasoconstrictor, also plays a role in the etiology of hypertension by mediating vascular tone through vasoconstriction [46 63]. Sex hormones influence the release of ET-1 in opposite ways, whereby testosterone causes an increase of ET-1 release and estrogen and progesterone cause inhibition of ET-1 release [46 63].

MENOPAUSE

The prevalence of hypertension increases with age in both sexes, but rates are lower in premenopausal female compared to age-matched male [64]. However, menopause initiates a rise in hypertension rates in female and the drop in estrogen relates to an increased risk on development of hypertension. Eventually, this rise results in higher hypertension rates in female compared to male after the age of 60 [39 65 66]. Clinical data has revealed that estrogen plays a key role in this finding due to exerting diverse hypertension preventing cardiovascular effects, such as vasorelaxation, preventing vascular remodeling, inhibiting sympathetic activity and decreasing aortic stiffness via effects on the endothelium and vascular smooth muscle cells [67]. With a mean age of the subjects from the included studies of 65.1 $\pm$ 11.8 (SD) years, one can assume that most of the included female subjects in this study were postmenopausal and as such, in absence of the cardioprotective effects of estrogen, at increased risk of hypertension. This can be seen as a shortcoming of our evaluated sex differences, since our observations predominantly apply to postmenopausal female. Studies did not report on menopausal state of most included female nor did they discuss the consequences this had on the results and on the applicability of the outcomes in premenopausal female.

GUIDELINES

The European and American Guidelines for the management of arterial hypertension do not mention sex-specific treatment recommendations, except for pregnancy being a contraindication for ARBs, ACEIs and DIU [68] [69]. Most of the available guidelines recommend the same drug type and dose for both females and males with hypertension in all age groups [70].These recommendations were made despite pharmacological findings showing that with the same ARB dose higher maximum plasma concentrations are reached in female, most likely due to smaller distribution space, differences in body composition amongst body fat mass and lean body mass, and lower body weight. This could lead to higher plasma concentrations and duration of efficacy of ARBs in female [71 72]. Moreover, female had the lowest risk of adverse outcomes at doses half the guideline recommended ones compared to male [71]. With our review, regarding BP control, data suggest neither clinical difference between sexes, nor differences in dosage necessary to reach these effects. On the one hand, in view of the substantiated established sex-specific diversities future research is necessary to offer proof for the current universal treatment approach. On the other hand, our review indicates

comparable effects reached with comparable dosages and treatment duration, suggesting universal treatment to be sufficient. This study supports the hypothesis that females will have the same outcome as males on equivalent doses of ARBs and raises the question if pharmacodynamic and pharmacokinetic established sex differences actually have a clinically significant impact on cardiovascular outcome effects between female and male.

STRENGTH AND LIMITATIONS

There are some limitations to mention. First, some included 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 slight female underrepresentation. Future studies may benefit from balancing the representation of female and male in their studies. Third, the mean age of almost all studies including female is around or above the median expected age of menopause, and, as such, may attenuate possible sex-related differences in BP response as a consequence of loss in protective effects of estrogen [65 66 73].

Conclusion and Recommendation

In individuals with hypertension, ARBs substantially lowered BP and heart rate without significant changes in LEVF. Although most included female individuals were past menopause, sex did not have a significant effect on absolute and relative changes.

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: wrote the initial draft of the paper, revised the paper and finalized the manuscript. SL: wrote the paper. MS, CG: initiated the project, developed the idea and coordinated the writing process. SL, MS, CH: wrote the paper and critically reviewed the content.

Data sharing statement

No individual patient data are included in this study. Search strategy and results of included papers are presented within the manuscript and are available at the corresponding author upon request.

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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Appendix

Table 1 Characteristics of studies

Study	Patient	Ethnicity	ARB 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
						Total	M	F		Total	M	F					
Axelsson (2015)[21]	HTN, HF, LVH	-	Losartan (oral)	75	75	64	40	24	Placebo	69	46	23	51 (13.9)	372	RCT	SBP, DBP, LVEF	Echo
Baysal (2017)[22]	HTN	-	Telmisartan (oral)	80	100	39	22	17	Amlodipine	38	22	16	47.8 (9.9)	30	RCT	SBP, DBP	Sphygmomanometry, ECG, echo
Cottone (1998)[23]	HTN	-	Losartan (oral)	50	50	16	16	0	-	-	-	-	42 (16)	180	Case control study	SBP, DBP	Echo
Cuocolo (1999)[24]	HTN	-	Valsartan (oral)	120	37.5	24	16	8	Enalapril	24	16	8	47 (8)	28	RCT, crossover	LVEF	Sphygmomanometry, ECG, echo
Kasanuki (2009)[25]	HTN, DM, CAD	-	Candesartan (oral)	8	25	1024	838	186	Other antihypertensives	1025	806	219	64.8 (9.2)	1440	RCT	SBP, DBP	Sphygmomanometry
Lee (2012)[26]	HTN, DM, LVH	-	Fimasartan (oral)	90	75	247	168	79	-	-	-	-	53.8 (9.2)	168	RCT	SBP, DBP, HR	Sphygmomanometry
			Losartan (oral)	75	75	238	167	71									
Malmqvist (2001)[27]	HTN, DM, LVH	W	Irbesartan (oral)	225	75	56	36	20	Atenolol	58	40	18	54.5 (9.3)	336	RCT	MAP, SBP, DBP, HR, LVEF	Sphygmomanometry, echo
Mehlum (2020)[28]	HTN, DM, HF, MI, LVH	W, B	Valsartan (oral)	10	3.1	7519	4332	3187	Amlodipine	7477	4305	3172	67 (14)	183	RCT	MAP, SBP, DBP, HR	Sphygmomanometry
Oh (2015)[291]	HTN, DM, HF	-	Valsartan (oral)	114.9	35.9	195	118	77	-	198	114	84	64.9 (11.6)	7	RCT	SBP, DBP	-
			Valsartan (oral)	128.8	40.3	195	118	77						90			

Table 1 Continued

Study	Patient	Ethnicity	ARB 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	Method of measurement
						Total	M	F		Total	M	F					
Os (2008)[30]	DM, HTN, CAD, LVH	W, B	Losartan (oral)	75	75	4605	2118	2487	Atenolol	4588	2112	2476	66.9 (7)	1825	RCT	SBP, DBP	ECG
Nalbantgil (2000[31]	HTN, LVH	-	Valsartan (oral)	80	25	20	20	0	Enalapril	20	20	0	54.1 (5.3)	180	RCT	SBP, DBP	Echo
Shin (2016)[32]	HTN, DM	-	Fimasartan (oral)	75	62.5	1396	748	648	-	-	-	-	56.2 (‡)	90	Prospective cohort	SBP, DBP, HR	-
Spoelstra-de Man (2006)[33]	DM, HTN	W	Candesartan (oral)	12	37.5	24	13	11	Hydrochlorothiazide or lisinopril	46	30	16	61.6 (6.9)	360	RCT	SBP, DBP, HR	Echo
Vescovo (1998)[34]	HTN, HF	-	Losartan (oral)	37.5	37.5	8	8	0	Enalapril	8	8	0	58.2 (4.5)	180	RCT	SBP, DBP, LVEF	ECG, echocardiogram
Voors (2010)[35]	HTN, DM, HF, MI	-	Eprosartan (oral)	500	83.3	47	17	30	-	50	19	31	64.5 (5.8)	180	RCT	SBP	Echo
Yamazaki (2007)[36]	HTN, LVH	-	Losartan (oral)	50	50	9	9	0		10	10	0	56.8 (7.5)	365	RCT, prospective cohort	LVM	ECG, echo
Zakynthinos (2005)[37]	HTN, LVH	-	Losartan (oral)	75	75	39	39	0	- -	29	29	0	45.9 (9.1)	243	RCT	SBP, DBP, HR, LVM	Echo

* Percentage of maximal dosage for the indication hypertension. Valsartan 320 mg/day orally (1); eprosartan 600 mg/day orally (2); fimasartan 120 mg/day orally (3); irbesartan 300 mg/day orally (4); losartan 100 mg/day orally (7); telmisartan 80 mg/day orally (8); candesartan 32 mg/day orally (13).
† Control group: other antihypertensive treatment (other than ARBs, ACE inhibitors, diuretics, beta blockers, calcium channel blockers), placebo or non-drug intervention.
‡ SD not reported.
Data presented as mean ± SD or percentages. B = black, CAD = coronary artery disease, DBP = diastolic blood pressure, DM = diabetes mellitus, 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, W = white.

Table S1 Literature search: strategy for PubMed (NCBI) and Embase (Ovid) databases

Search PubMed	Search Embase
Component 1: Antihypertensive medication: "diuretics"[Mesh] OR "adrenergic beta-antagonists"[Mesh] OR "beta blockers" [Title/Abstract] OR "Antihypertensive agents"[Mesh] OR "BP lowering therapy" [Title/Abstract] OR "antihypertensive medication" [Title/Abstract] OR "antihypertensive therapy" [Title/Abstract] OR "angiotensin-converting enzyme inhibitors"[Mesh] OR "ACE inhibitors" [Title/Abstract] OR "Angiotensin receptor antagonists"[Mesh] OR "angiotensin receptor blockers" [Title/Abstract] OR "sympatholytics"[Mesh]OR "Calcium Channel Blockers"[Mesh]	**Component 1: Antihypertensive medication** exp diuretic agent/ or exp beta adrenergic receptor blocking agent/ or exp adrenergic receptor blocking agent/ or exp antihypertensive agent/ or exp dipeptidyl carboxypeptidase inhibitor/ or exp angiotensin receptor antagonist/ or exp calcium channel blocking agent.ti,ab.
Component 2: Cardiac geometry: "ventricular remodeling"[Mesh] OR "ventricular remodeling" [Title/Abstract] OR "cardiac remodeling" [Title/Abstract] OR "cardiac adaptation" [Title/Abstract] OR "LV geometry" [Title/Abstract] OR "left ventricular geometry" [Title/Abstract] OR "cardiac geometry" [Title/Abstract] OR "cardiac dimension" [Title/Abstract] OR "left ventricle remodeling "[Title/Abstract] OR " Hypertrophy, Left Ventricular "[Mesh] OR "left ventricular hypertrophy" [Title/Abstract] OR "echocardiography"[Mesh] OR Echocardiography [Title/Abstract] OR "left ventricular mass" [Title/Abstract] OR "left ventricular mass index" [Title/Abstract] OR "relative wall thickness" [Title/Abstract] OR "concentric cardiac remodeling" [Title/Abstract] OR "eccentric cardiac remodeling" [Title/Abstract]	**Component 2: Cardiac geometry** exp heart ventricle remodeling/ or (ventricular remodeling or cardiac remodeling or cardiac adaptation or LV geometry or left ventricular remodeling or cardiac geometry or cardiac dimension).ti,ab. or exp echocardiography/ or echocardiography.ti,ab.
Component 3: Heart failure: "Heart Failure"[Mesh] OR "Heart Failure, Systolic "[Mesh]	**Component 3: Heart failure** exp heart failure.ti,ab.
Component 4: Diastolic dysfunction: "heart failure, diastolic" [Mesh] OR "diastolic dysfunction" [Title/Abstract]	**Component 4: Diastolic dysfunction** exp diastolic dysfunction/ or diastolic function.ti,ab.
Component 5: Myocardial infarction: "myocardial infarction" [Mesh] OR "myocardial infarction" [Title/Abstract] OR "acute myocardial infarction" [Title/Abstract] OR "heart attack" [Title/Abstract]	**Component 5: Myocardial infarction** exp heart infarction.ti,ab.
Component 6: CVA: Stroke [Mesh] OR "cerebrovascular accident" [Title/Abstract] OR "acute cerebrovascular accident" [Title/Abstract] OR "acute cerebrovascular insult" [Title/Abstract]	**Component 6: CVA** exp cerebrovascular accident.ti,ab.

Combination search terms: component 1 AND (component 2 OR component 3 OR component 4 OR component 5 OR component

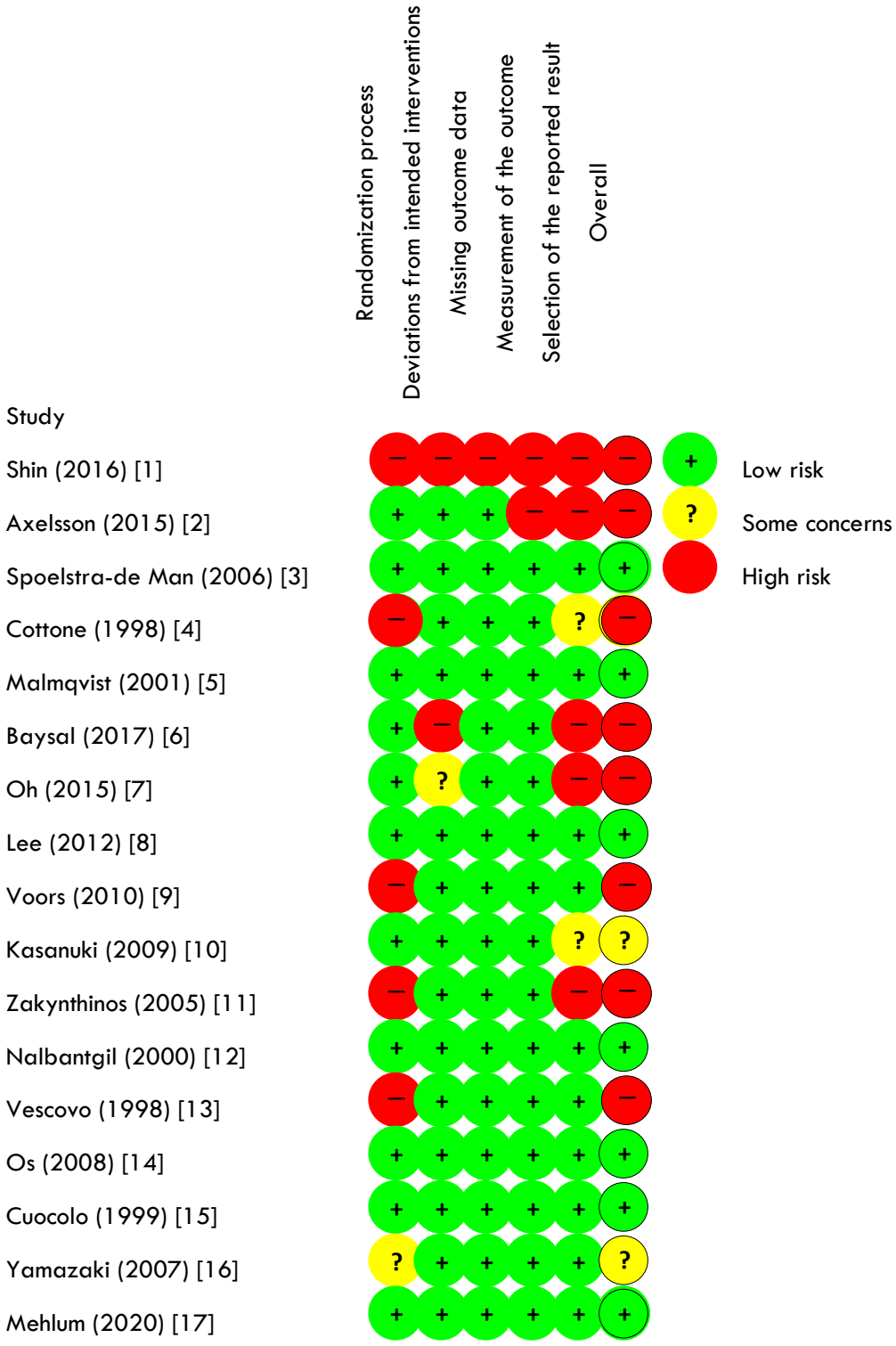

Figure S2 Risk-of-bias assessment within studies

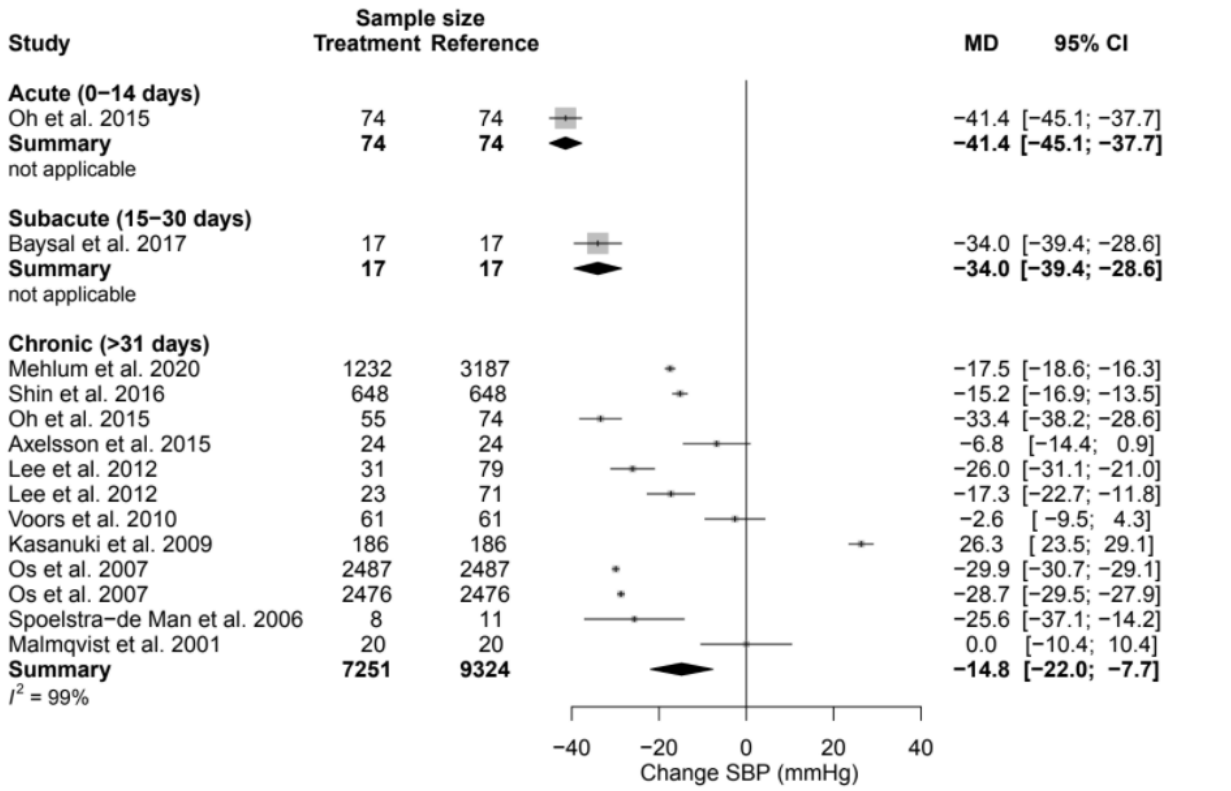

Figure S5 Forest plot of systolic BP (SBP) change in mmHg after acute, subacute and chronic ARB use compared to baseline for females. MD = mean difference

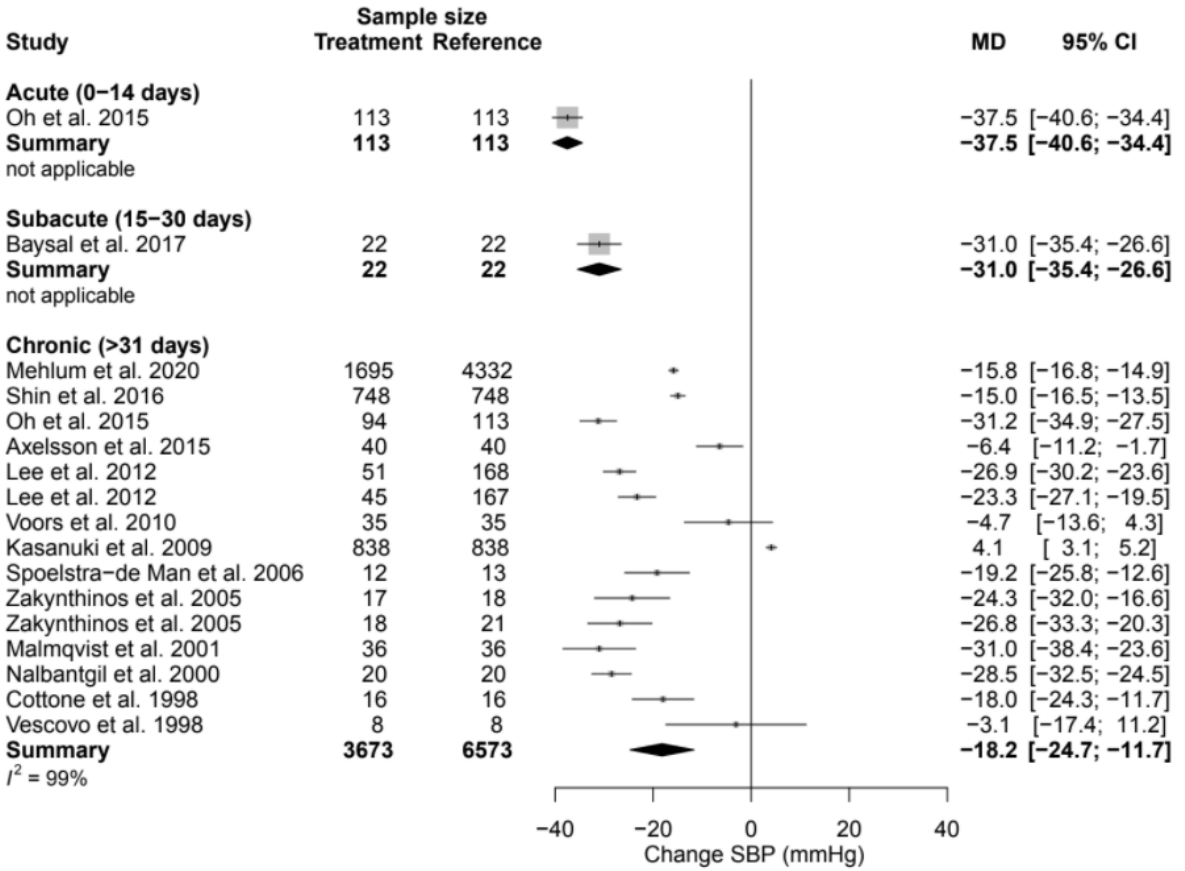

Figure S6 Forest plot of systolic BP (SBP) change in mmHg after acute, subacute and chronic ARB use compared to baseline for males. MD = mean difference

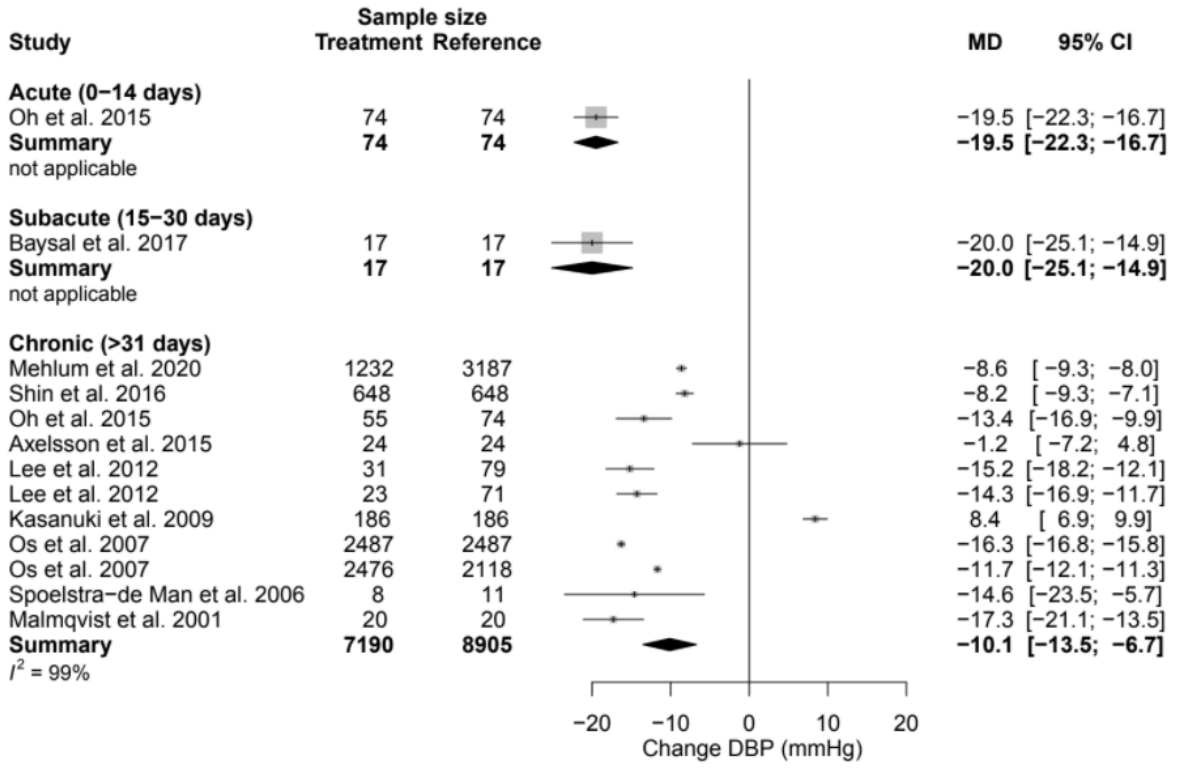

Figure S8 Forest plot of diastolic BP (DBP) change in mmHg after acute, subacute and chronic ARB use compared to baseline for females. MD = mean difference

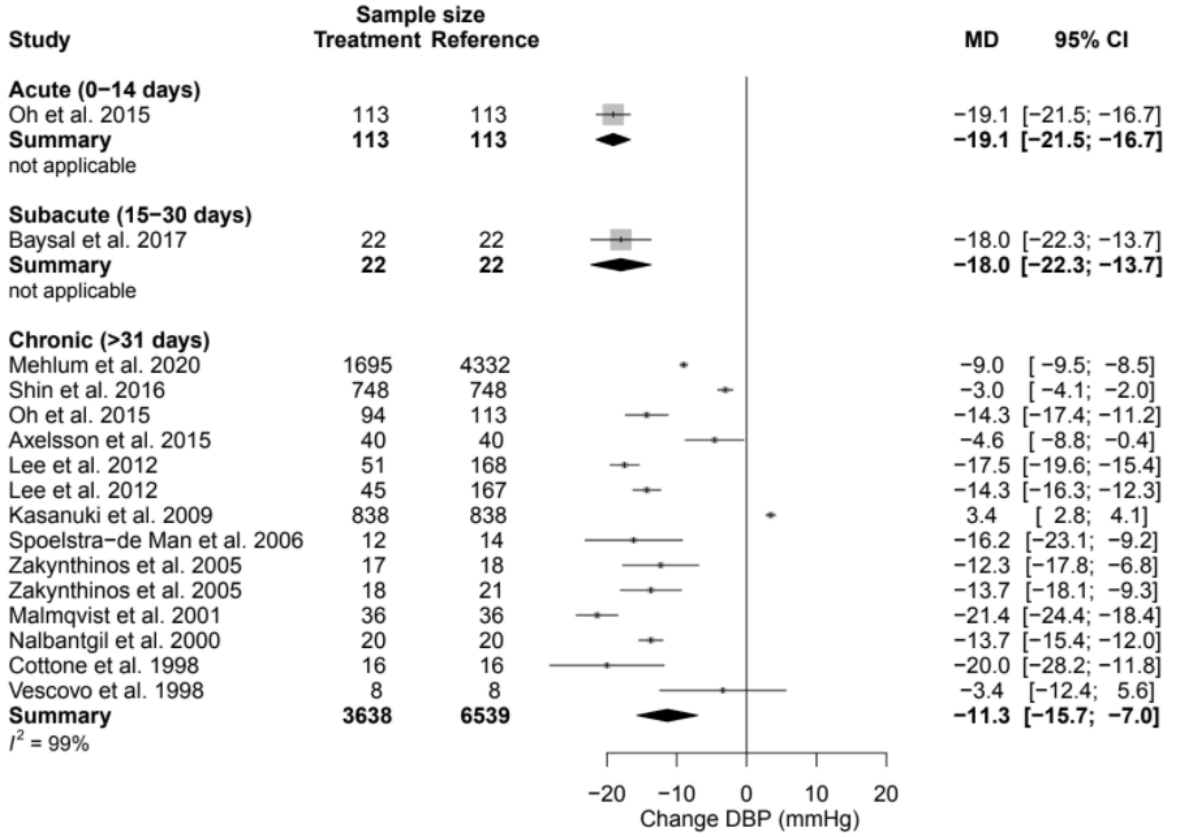

Figure S9 Forest plot of diastolic BP (DBP) change in mmHg after acute, subacute and chronic ARB use compared to baseline for males. MD = mean difference

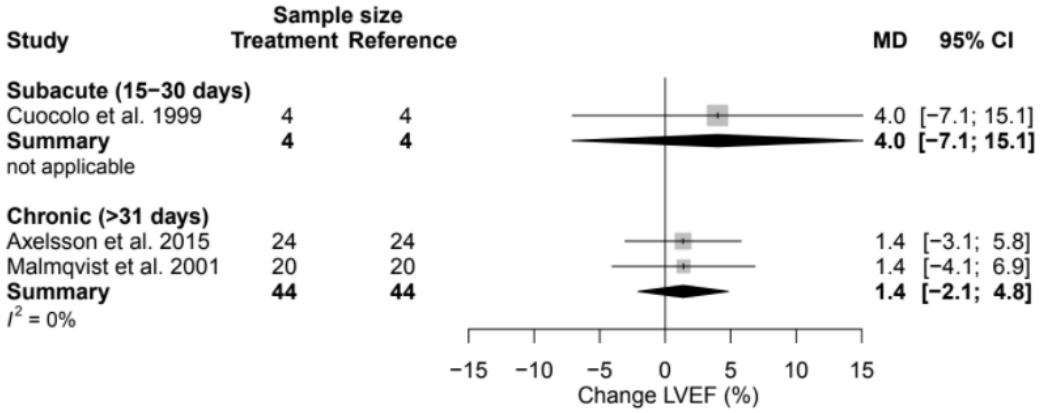

Figure S12 Forest plot of left ventricular ejection fraction (LVEF) change in % after subacute and chronic ARB use compared to baseline for females. MD = mean difference

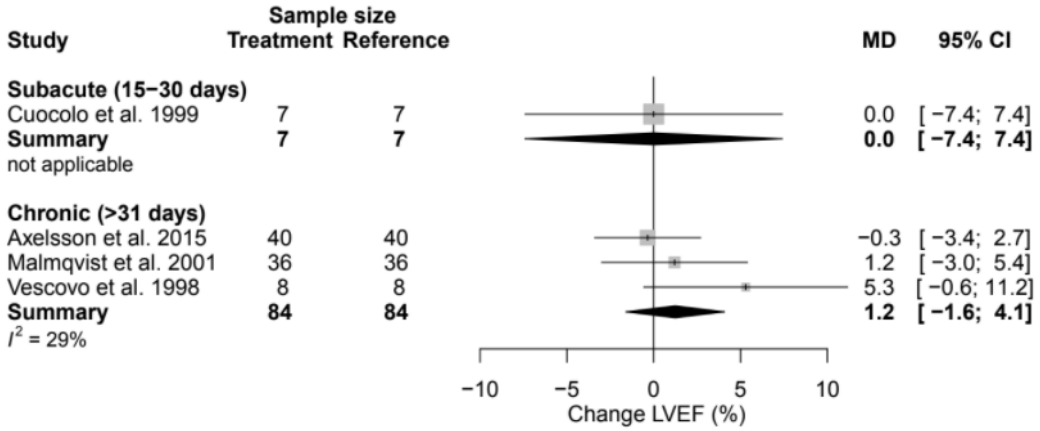

Figure S13 Forest plot of left ventricular ejection fraction (LVEF) change in % after subacute and chronic ARB use compared to baseline for males. MD = mean difference

Table S2 Publication bias

Parameter	Females	Males
MAP (mmHg)	*	*
SBP (mmHg)	0.2598	0.0727
DBP (mmHg)	0.6140	0.0826
HR (bpm)	0.6842	0.0826
LVEF (%)	0.1544	0.4322
LVM (g)	N=0	0.6577

*Assessment not possible

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