Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: November 30, 2023

Citation: Vaes, E., W., P., et al., 2024. Sex differences in the efficacy of diuretics in the treatment of hypertension; a systematic review and meta-analysis. Medical Research Archives, [online] 11(11). https://doi.org/10.18103/mra.v11i11.4269

DOI: https://doi.org/10.18103/mra.v11i11.4269

ISSN: 2375-1924

RESEARCH ARTICLE

Sex differences in the efficacy of diuretics in the treatment of hypertension; a systematic review and meta-analysis

Esmée W. P. Vaes[1,2,3*], Nick Wilmes[1,4], Daniek A. M. Meijs[1,4], Sophie A. J. S. Laven[1], Maud A. M. Vesseur[1], Zenab Mohseni-Alsalhi[1,5], Eveline M. van Luik[1], Sander de Haas[1,5], Marc E. A. Spaanderman[1,5,6], Chahinda Ghossein-Doha[3,4,7]

[1]Department of Obstetrics and Gynecology, Maastricht University Medical Center (MUMC+), 6229 ER Maastricht, The Netherlands.
[2]Department of Family Medicine, Care and Public Health Research Institute, Maastricht University, 6229 ER Maastricht, The Netherlands.
[3]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, University Utrecht, 3508 GA Utrecht, The Netherlands.
[4]Cardiovascular Research Institute Maastricht, School for Cardiovascular Diseases, Maastricht University, 6229 ER Maastricht, The Netherlands.
[5]GROW-School for Oncology and Developmental Biology, Maastricht University, 6229 ER Maastricht, The Netherlands.
[6]Department of Obstetrics and Gynecology, Radboud University Medical Center, 6525 GA Nijmegen, The Netherlands.
[7]Department of Cardiology, Maastricht University Medical Center (MUMC+), 6229 ER Maastricht, The Netherlands.

*esmee.vaes@maastrichtuniversity.nl

ABSTRACT

Background: Pharmacological treatment of high blood pressure is considered essential in the prevention of cardiovascular morbidity and mortality, but sex differences may disturb effectiveness. The aim of this systematic review and metaanalysis was to evaluate possible differences in effects for diuretics on blood pressure, heart rate and cardiac function in female compared to male hypertensive individuals.

Methods: We performed a systematic review and meta-analysis on studies on diuretics from 1945 to May 2020. Studies had to present both baseline and follow-up measurements of the interested outcome variables and present data sex-stratified. Mean differences were calculated using a random-effects model.

Results: Eighteen studies investigating diuretics were used in this review. The effect of diuretics on blood pressure was clinically significant in both females and males and more profound in chronic treatment. Heart rate and left ventricular ejection fraction did not change significantly throughout treatment in both sexes, but cardiac output decreased significantly in females. Changes in left ventricular mass were only significant in males.

Conclusion: Diuretics decreased blood pressure in both sexes, especially when used chronically. Nonetheless, sex depending differences on blood pressure, cardiac output and left ventricular mass may suggest diversity in response to diuretics, implying the importance of considering sex-specific treatment strategies.

Keywords: hypertension; cardiovascular disease; diuretics; sex differences; systematic review; meta-analysis.

Introduction

To date, cardiovascular disease (CVD) is the number one cause of death worldwide[1]. Hypertension is considered the leading threat towards the development of CVD. Although the prevalence of CVD is higher in males, females have, on the contrary, poorer prognosis and higher mortality rate[2]. Unrecognized complaints that may relate to disparity in underlying pathophysiological mechanisms are thought to relate to delayed diagnostic trajectories, unsuited treatment and with it remote health outcome (3). Increasing awareness regarding exposure to cardiovascular risk factors, amongst family history, lifestyle related diseases, cardiovascular and cardiometabolic pregnancyrelated complications, preeclampsia, fetal growth restriction and gestational diabetes mellitus, have not yet resulted in improved CVD prevention in females[3-5].

Besides lifestyle and dietary interventions, one of the main pillars for the prevention of CVD is medicament treatment of high blood pressure.

Amongst five most commonly used antihypertensive medication, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers and calcium channel blockers, diuretics are the longest existing antihypertensive medication type[6]. Thiazides, loop diuretics, and potassium-sparing diuretics are the three main classes of diuretics, each exerting their effect on a different target in the renal tubules[7,8]. Thiazide diuretics inhibit the Na+/2Cl- transport in the early distal convoluted tubule. Loop diuretics inhibit the Na+/K+/2Cl- exchange in the thick ascending limb of the loop of Henle. Finally, the potassiumsparing diuretics amiloride and triamterene inhibit the epithelial sodium channel in the cortical collecting duct while the potassiumsparing diuretics spironolactone and eplerenone inhibit the aldosterone receptor also in the cortical collecting duct. By inhibiting these cellular exchange mechanisms, diuretics enhance natriuresis and diuresis, thereby lowering circulatory volume and with it blood pressure[8,9]. In these, not only sex disparity in response to diuretics exist, diuretics have also been linked to less user-safety in females as compared to males. Differences in body composition, pharmacodynamics and pharmacokinetics are thought to underlie these disparities[10-13].

Since the implementation of diuretics, multiple studies have investigated the effects of diuretics on blood pressure and other cardiovascular and hemodynamic variables[14,15]. Although diuretic treatment seems to be effective in treating hypertension, not much attention has been paid to possible differences in treatment effect between females and males. To this end, we performed a systematic review and metaanalysis comparing the effectiveness of acute (014 days), subacute (15-30 days), and chronic (>30 days) diuretic treatment in female versus male adults. The variables of primary interest were systolic and diastolic blood pressure, mean arterial blood pressure and heart rate. Variables of secondary interest were cardiac output, left ventricular ejection fraction, and left ventricular mass.

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 diuretics. PRISMA reporting guidelines were taken into account (Table S1). 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 haemodynamic variables using PubMed (NCBI) and Embase (Ovid) databases. PubMed and Embase provided publications ranking from 1945 to May 2020. The search terms are presented in Table 1. The search strategy focused on the effect of the five commonly used antihypertensive drugs on blood pressure, left ventricular geometry and left ventricular function. The search limits used were 'humans' and 'journal article'.

Table 1 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 "blood pressure 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"	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.

[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 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.

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 selections 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 (diuretics, beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and calcium channel blockers (CCB)), 2) human studies, 3) included adults > 18 years of age, 4) articles written in English or Dutch, 5) with a suitable study design (randomized controlled trials (RCTs), prospective and retrospective cohort studies).

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

placebo, other antihypertensive medication group), 7) the outcome was not related to one of the predefined variables (systolic and diastolic blood pressure, heart rate, cardiac output, left ventricular ejection fraction, and/or left ventricular mass), 8) data were not reported as standard deviation (SD), standard error (SE), or 95% confidence interval (95% CI), 9) no specific dose and duration information were registered, 10) participants were undergoing invasive operations, participants who were performing exercise during measurements, or undergoing dialysis or chemotherapy. If studies presented their data differently (for example, median with interquartile range), mean values with SD were requested from the authors by email.

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 e-mailed or approached 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 (>30 days) therapy. Study characteristics (sample size, control group, and study design), anthropometric data (age and ethnicity), intervention characteristics (dose, duration, and method of measurement), and effect measures (mean and SD at baseline and after diuretic intervention of the predefined variables) were collected in a predesigned format. The study results were separately extracted for females and males. In this systematic review only blood pressure data measured via non-invasive methods were extracted. For the other variables, multiple methods were allowed.

QUALITY ASSESSMENT

The included studies were assessed for quality and risk of bias using the Cochrane recommended Risk of Bias 2 (RoB2) tool[16]. 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 judgment of “Low risk of bias”, all domains had to receive this judgment. To receive an overall judgment 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 judgment 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[17]. Changes in the cardiovascular

and hemodynamic variables from baseline were separately analyzed for males and females using a random-effects model as described by DerSimonian and Laird[18]. Because the included studies had some variation in study population and design, the random-effects model was chosen to account for this interstudy variation (19). 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 I2 statistic, the ratio between heterogeneity and variability, was calculated as a measure of consistency and expressed as percentage in the forest plots. I2 is able to distinguish heterogeneity in data from solely sampling variance[(19)]. Interpretation of I2 was based on the guidelines in the Cochrane Handbook for Systematic Review of Interventions[19]. Sources of clinical heterogeneity (diuretic class, treatment duration, and dosage) and methodological heterogeneity (quality of study) were investigated by meta-regression analyses using a mixed-effects model[(19)]. The Egger's regression test for funnel plot asymmetry was performed to test the presence of publication bias. For the meta-analyses and meta-regression analyses, the meta package in the statistical programme R version 4.0.3. was used[20,21]. A significance level of 5% was used in all analyses.

Results

STUDY SELECTION

The literature search provided a total of 73,867 unique records (Figure 1). After the title-abstract selection, 58,737 records were excluded (79.5%) resulting in 15,130 eligible articles for the fulltext selection. After the full text of these articles was examined, 14,925 articles (98.6%) met at least one exclusion criterium. These articles were excluded for several reasons, which are further detailed in Figure 1. If needed, additional information was requested by emailing study authors or articles dated from 1980 or earlier and were therefore not emailed. Eventually, a total of 205 articles were included for the whole series of which 18 articles reported on diuretics and included in this study.

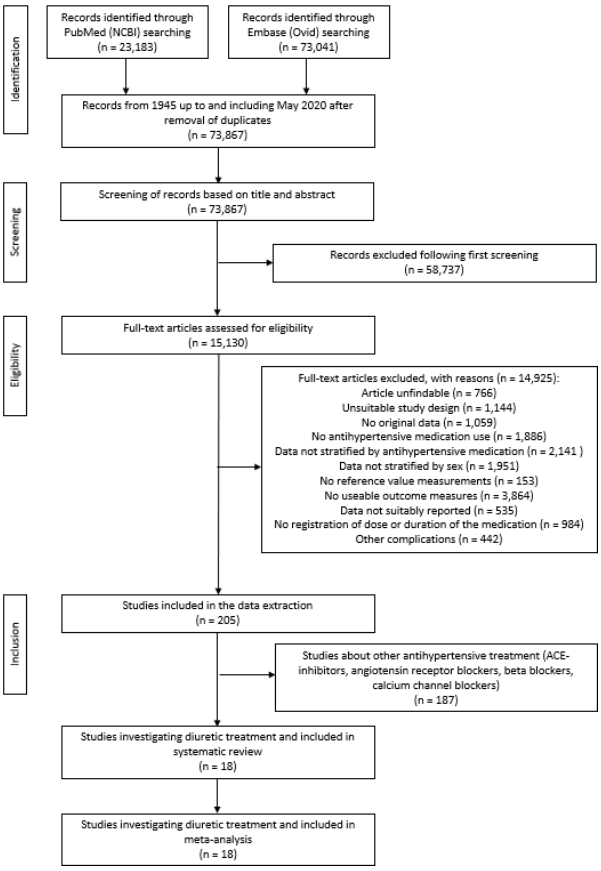


Figure 1 Flowchart of study selection and inclusion after systematic literature search

STUDY CHARACTERISTICS

Study characteristics and anthropometric data of the study participants are summarized in Table S2. In total, data of 6,913 participants

using diuretics were included in this meta-analysis, of whom 83 were females (1.2%). The study of Dorsch *et al.* [22] including many male participants causes a significant discrepancy between the number of males and females included in this meta-analysis. The mean age of the participants from the included studies was 49.2 ± 8.6 (SD) years.

Eleven studies reported on thiazide diuretics (nine on hydrochlorothiazide[22-30] and two on chlorthalidone[22,31], eight on loop diuretics (six on furosemide[32-37], one on piretanide[35], and one on torasemide[37]), and two on potassium-sparing diuretics (spironolactone[38,39]). The remaining two classes of diuretics, osmotic and carbonic anhydrase diuretics, were not studied in the selected studies in this systematic review and meta-analysis.

Systolic blood pressure was reported in 12 studies[22-24,26-32,36,37], diastolic blood pressure in 13 studies[23-33,36,37], heart rate in 11 studies[24,26-28,31,33-37,39], cardiac output in four studies[23,33,35,36], left ventricular ejection fraction in two studies[31,32], and left ventricular mass in five studies[26,28,31,32,38].

Five studies measured the acute effects of diuretic treatment (follow-up between 0 and 14 days)[33-36,39]. Two studies measured a subacute effect (follow-up between 15 and 30 days)[29,30]. The remaining 11 studies measured a chronic effect which means a follow-up period of 31 days or longer[22-28,31,32,37,38].

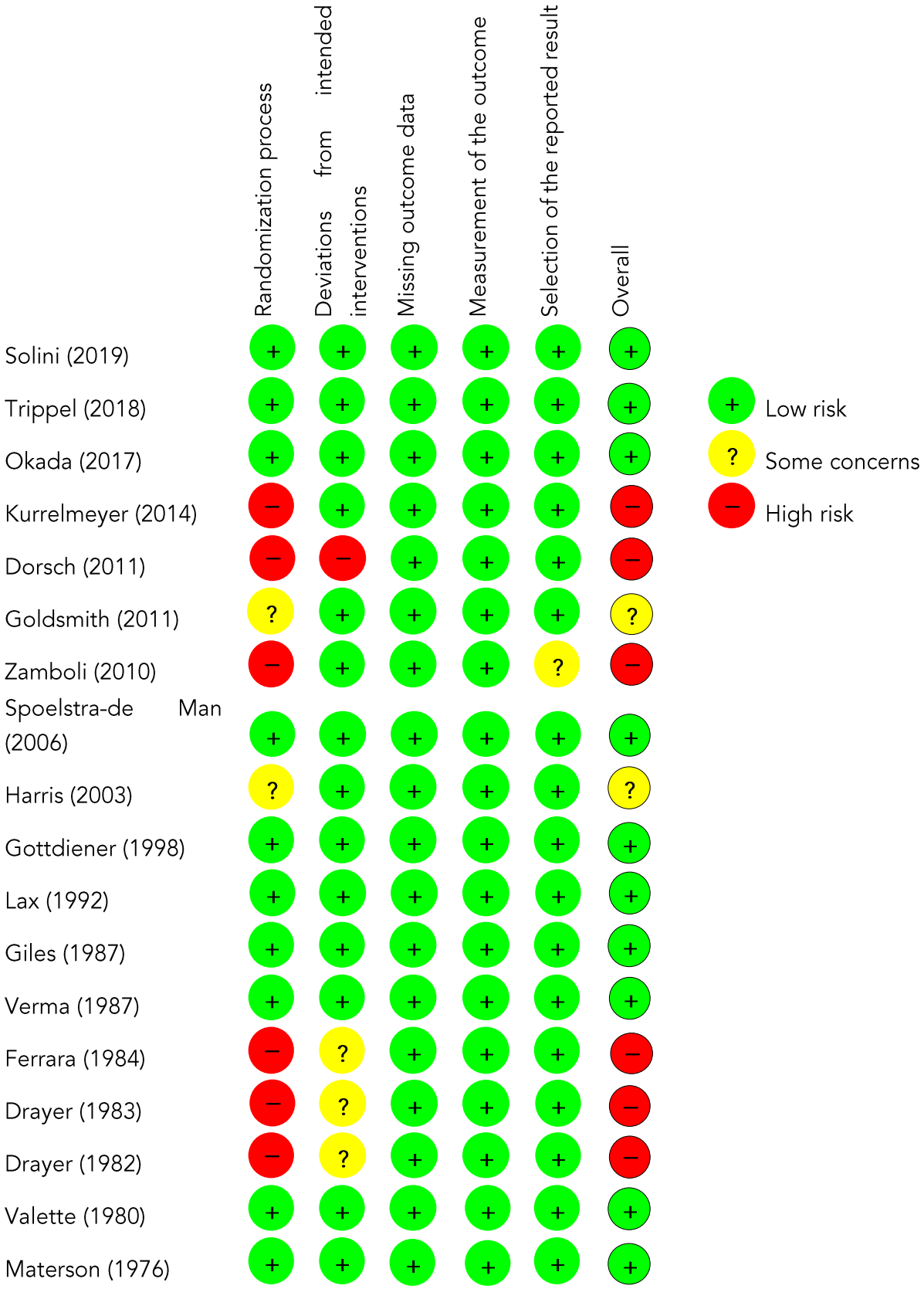
Of the included studies, 15 were RCTs[23-26,29-39], two prospective cohort studies[27,28], and one retrospective cohort study[22].

Five studies included males and females but did not report the outcomes separated for sex[23,24,30,32,37]. Sex-specific data was provided by these authors via email. Two studies included only females[33,38], and 11 studies included only males[22,25-29,31,34-36,39].

QUALITY ASSESSMENT

Table 2 provides a summary of the risk-of-bias assessment within studies according to the RoB2 tool. Ten out of 18 articles had a low overall risk of bias[23-26,29,30,33-35,37]. Six studies had a high overall risk of bias[22,27,28,31,32,38]. The two prospective cohort studies[27,28] and the retrospective cohort study[22] had a high risk of bias due to lacking randomization and blinding. The remaining two studies were scored as having some concerns[36,39].

Table 2 Risk-of-bias assessment within studies



SYSTOLIC BLOOD PRESSURE

The mean systolic blood pressure (SBP) in the studies population was 144.3 mmHg (95% CI, 133.5; 155.0) in females (n=44) and 144.0 mmHg (95% CI, 139.8; 148.2) in males (n=6682) at baseline (p = 0.9656). The mean difference and relative percentual change from baseline in percentages for SBP are reported in Table 3 and Figure 2. SBP decreased by 17.9 mmHg (95% CI, -24.4; -11.5)(-12.1% (95% CI, -16.4; -7.7)) in females after diuretic therapy, which was greater than the effect observed in males (-8.2 mmHg (95% CI, -11.4; -4.9))(-5.7% (95% CI, -7.9; -3.4)) (p = 0.0081). The mean difference for SBP by treatment duration is reported in Table 4. Most studies reported chronic effects of diuretics on SBP. The observed decrease in SBP is most present in the chronic phase for both females and males (Figures 3, 4, 5). Heterogeneity was low in female data (I^2 = 5%) and substantial in male data (I^2 = 75%). Of the clinical (diuretic class, treatment duration, and dosage) and methodological (study quality) sources of heterogeneity only the diuretic class furosemide significantly affected the change in SBP (Table 5). Egger's regression test for funnel plot asymmetry was statistically significant for females (p = 0.0359) and not significant for males (p = 0.2782). The corrected mean difference for females was -21.8 mmHg (95%, -29.1; -14.4).

Table 3 Pooled changes in cardiovascular and haemodynamic parameters for females and males

Parameter		Females	Males
SBP (mmHg)	MD %	-17.9 (-24.4; -11.5) -12.1 (-16.4; -7.7)	-8.2 (-11.4; -4.9) -4.2 (-5.9; -2.5)
DBP (mmHg)	MD %	-6.0 (-11.0; -1.0) -7.6 (-13.9; -1.2)	-2.7 (-5.3; -0.1) -2.0 (-4.0; -0.1)
HR (bpm)	MD %	-3.8 (-9.3; 1.6) -5.1 (-12.3; 2.2)	0.6 (-1.4; 2.6) 0.4 (-1.0; 1.9)
CO (L/min)	MD%	-0.7 (-1.2; -0.2) -15.3 (-27.0; -3.6)	-0.1 (-0.8; 0.6) -1.6 (-11.4; 8.2)
LVEF (%)	MD%	1.0 (-5.1; 7.1) 1.6 (-8.3; 11.5)	1.4 (-4.7; 7.4) 1.5 (-5.1; 8.2)
LVM (g)	MD%	-1.6 (-24.3; 21.0) -0.8 (-12.5, 10.8)	-25.5 (-44.4; -6.6) -6.8 (-11.8; -1.8)

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

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

Parameter		Females	Males
SBP (mmHg)	MD acute	-	12.9 (-12.2; 38.0)
	MD sub-acute	-17.0 (-39.6; 5.6)	1.7 (-4.0; 7.3)
	MD chronic	-17.4 (-25.1; -9.6)	-10.6 (-13.8; -7.4)
DBP (mmHg)	MD acute	-1.0 (-6.5; 4.5)	6.6 (-5.5; 18.7)
	MD sub-acute	-13.5 (-29.8; 2.8)	2.3 (-0.6; 5.2)
	MD chronic	-6.9 (-12.8; -1.1)	-4.7 (-7.9; -1.5)
HR (bpm)	MD acute	-4.0 (-11.0; 3.0)	0.0 (-3.1; 3.2)
	MD sub-acute	-	-
	MD chronic	-3.6 (-12.2; 5.1)	1.1 (-1.6; 3.8)
CO (L/min)	MD acute	-1.0 (-2.2; 0.2)	-0.6 (-1.6; 0.3)
	MD sub-acute	-	-
	MD chronic	-0.6 (-1.2; 0.0)	0.4 (-0.6; 1.3)

Values are reported as mean difference (MD) compared to baseline with 95% CI. Acute = 0-14 days, sub-acute = 15-30 days, chronic = >31 days, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, CO = cardiac output.

Table 5 P-values of meta-regression analysis

Sources of heterogeneity	SBP	DBP	HR	CO	LVM
Furosemide	0.0371	0.0336	0.6331	-	0.4811
Hydrochlorothiazide	0.1058	0.3358	0.9320	0.2453	0.6046
Torasemide	0.1766	0.0689	0.2640	-	-
Piretanide	-	-	0.9542	0.5001	-
Spironolactone	-	-	0.7705	-	0.3555
Low quality	0.3723	0.2923	0.2245	-	0.2758
Moderate quality	0.0960	0.1232	0.1796	0.5814	-
Treatment duration	0.4007	0.7066	0.2740	0.1502	0.2555
% max dose	0.9757	0.7937	0.5144	0.6394	0.3855

NB. Meta-regression analyses was not performed for left ventricular ejection fraction as only three articles were included.

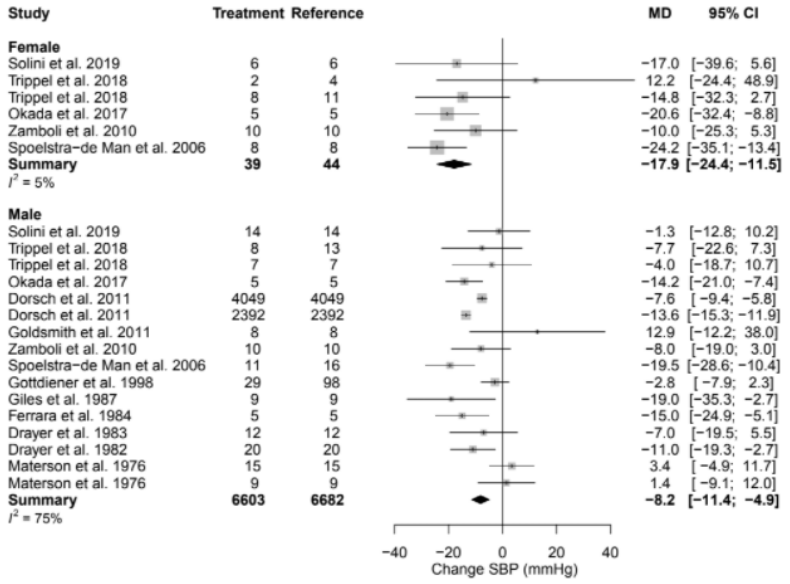


Figure 2 Forest plot of systolic blood pressure (SBP) change in mmHg after diuretic use compared to baseline for females and males. MD = mean difference

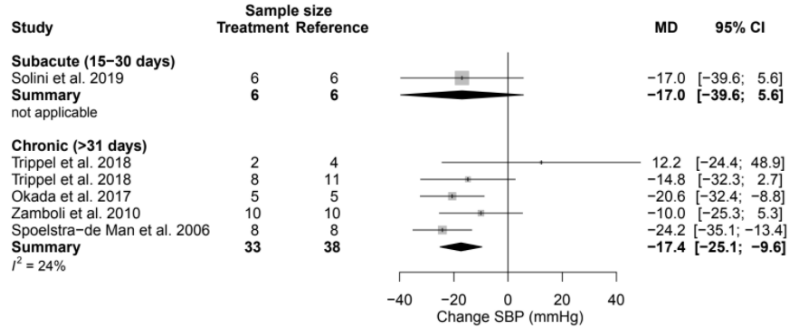


Figure 3 Forest plot of systolic blood pressure (SBP) change in mmHg after acute, sub-acute and chronic diuretic use compared to baseline for females. MD = mean difference

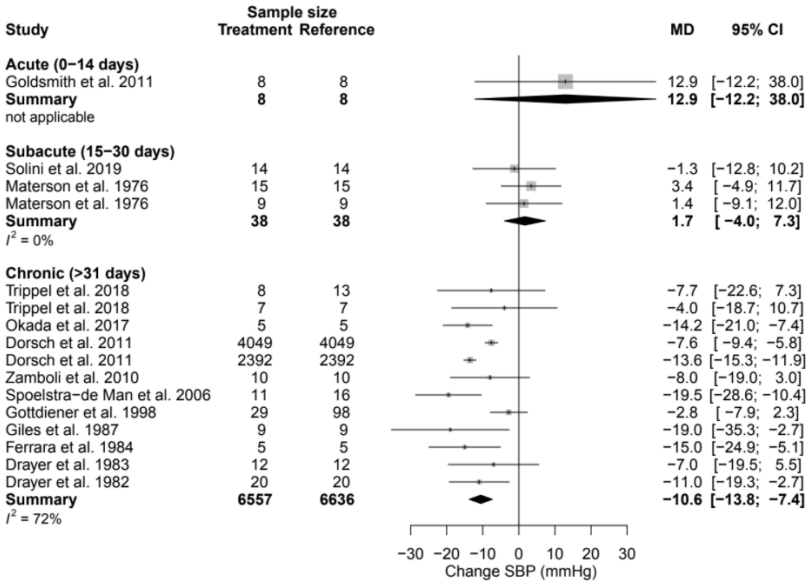


Figure 4 Forest plot of systolic blood pressure (SBP) change in mmHg after acute, sub-acute and chronic diuretic use compared to baseline for males. MD = mean difference

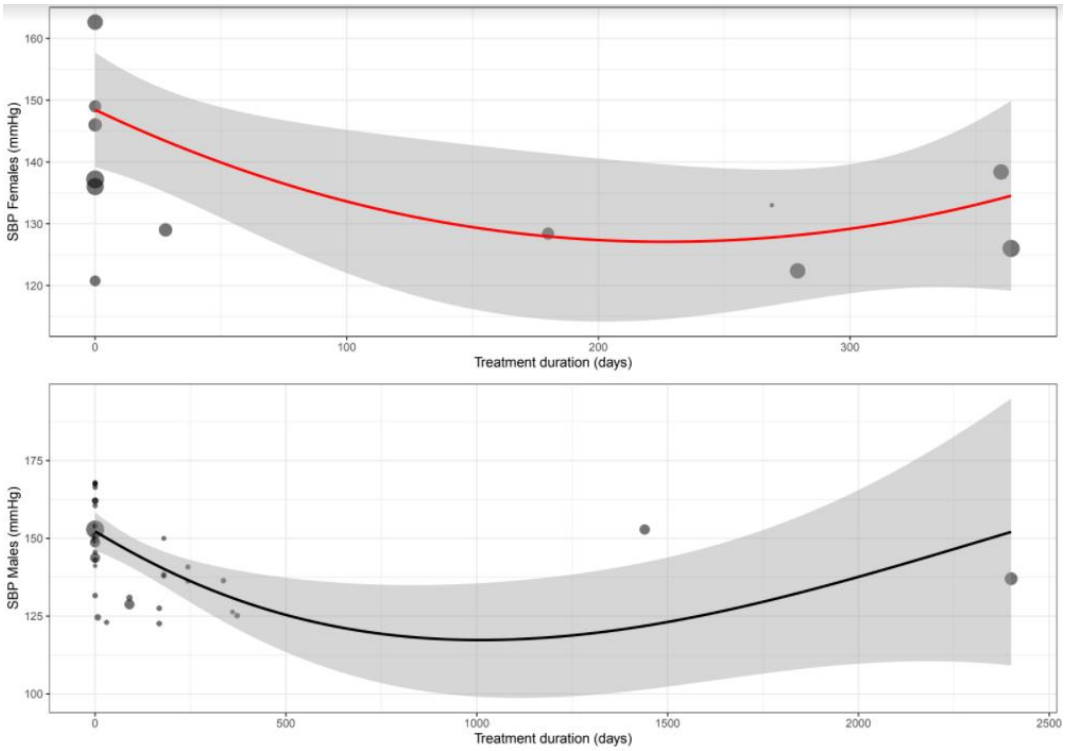


Figure 5 Meta-regression curve of systolic blood pressure (SBP) by treatment duration (days). Every circle is representing one article and the size represents the number of participants included in the study, shown as a small or larger circle

DIASTOLIC BLOOD PRESSURE

The mean diastolic blood pressure (DBP) in the studies population was 78.7 mmHg (95% CI, 70.4; 86.9) in females (n=59) and 90.6 mmHg (95% CI, 85.3; 95.9) in males (n=241) at baseline and was statistically different between the sexes (p = 0.0166). Although DBP decreased by 6.0 mmHg (95% CI, -11.0; -1.0)(-7.6% (95% CI, -13.9; -1.2)) in females and by 2.7 mmHg (95% CI, -5.3; -0.1) (-3.0% (95% CI, -5.8; -0.1)) in males (Table 3, Figure 6), this change was not statistically significant between sexes (p = 0.2619). The mean difference for DBP by treatment duration is reported in Table 4. Most articles were interested in a chronic effect of diuretics on DBP. The found decrease in DBP is most visible in the chronic phase for both females and males (Figures 7, 8, 9). Heterogeneity was moderate in female data (I^2 = 49%) and substantial male data (I^2 = 70%). The clinical source of heterogeneity detected by meta-regression analysis was furosemide (Table 5). Egger's regression test for funnel plot asymmetry was not statistically significant for females (p = 0.9414) and males (p = 0.5006).

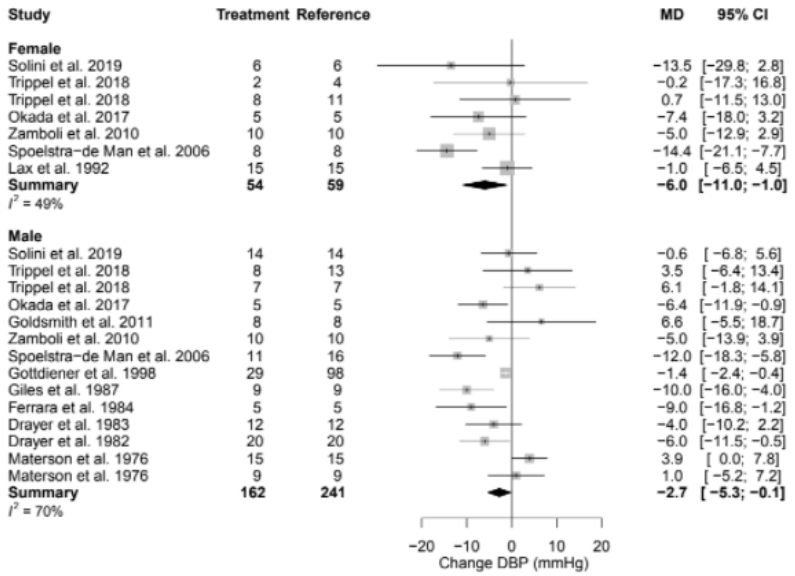


Figure 6 Forest plot of diastolic blood pressure (DBP) change in mmHg after diuretic use compared to baseline for females and males. MD = mean difference

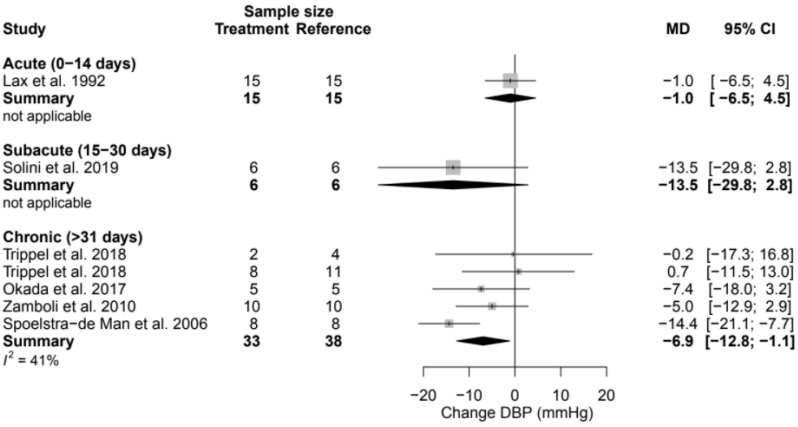


Figure 7 Forest plot of diastolic blood pressure (DBP) change in mmHg after acute, sub-acute and chronic diuretic use compared to baseline for females. MD = mean difference

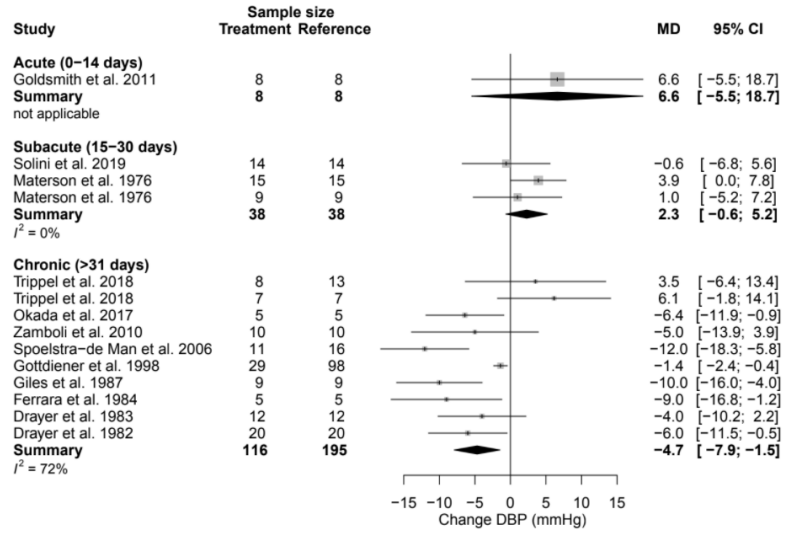


Figure 8 Forest plot of diastolic blood pressure (DBP) change in mmHg after acute, sub-acute and chronic diuretic use compared to baseline for males. MD = mean difference

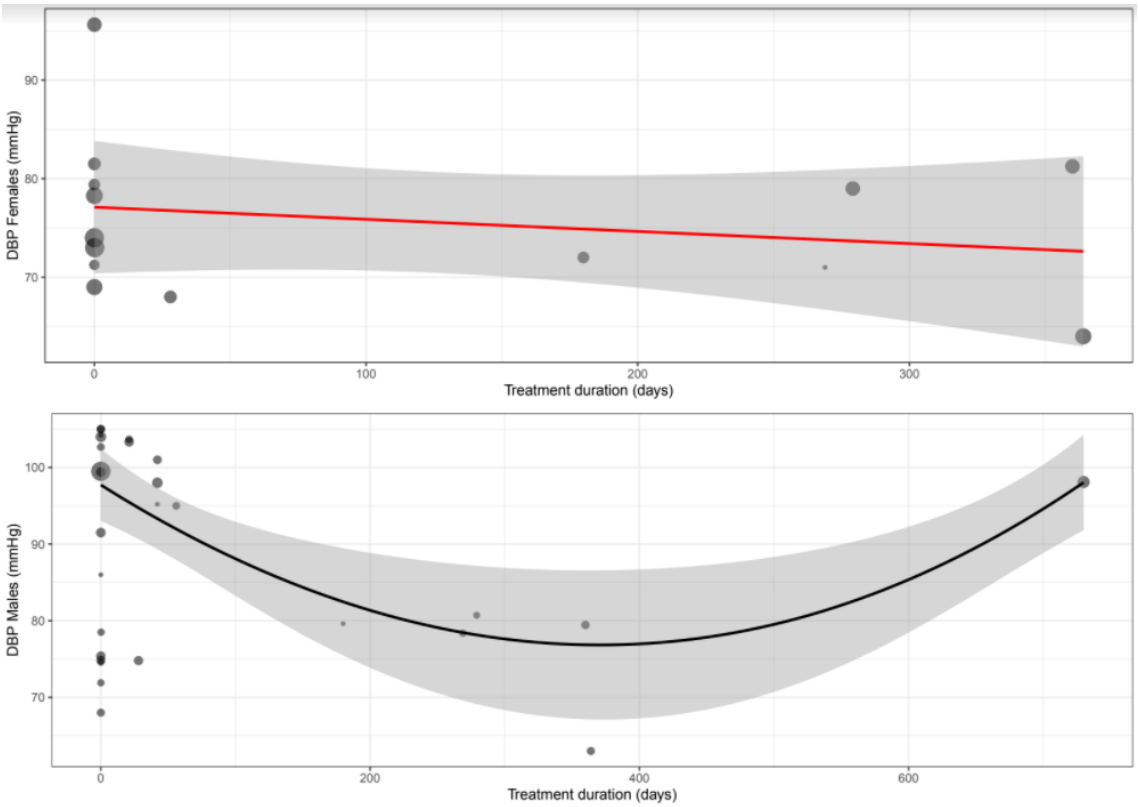


Figure 9 Meta-regression curve of diastolic blood pressure (DBP) by treatment duration (days). Every circle is representing one article and the size represents the number of participants included in the study, shown as a small or larger circle

HEART RATE

The mean heart rate (HR) in the studies population was 74.8 bpm (95% CI, 71.2; 78.4) in females (n=34) and 91.6 bpm (95% CI, 66.7; 116.6) in males (n=236) at baseline (p = 0.1916). An opposite effect between females and males seemed to be present in HR after diuretic use, although not statistically significant (p = 0.1335). HR changed insignificantly by -3.8 bpm (95% CI, -9.3; 1.6)(-5.1% (95% CI, -12.3; 2.2)) in females, and 0.6 bpm (95 %CI, -1.4; 2.6)(0.6% (95% CI, -1.3; 2.5)) in males (p = 0.1335) (Table 3, Figure 10). The mean difference for HR by treatment duration is reported in Table 4. There is no trend observed in change in HR by treatment duration (Figures 11, 12). Clinical and methodological heterogeneity did not affect the change in HR (Table 5). Egger's regression test for funnel plot asymmetry was statistically significant for males (p = 0.0200) and not for females (p = 0.6013). The corrected mean difference for males was -0.5 bmp (95% CI, -2.4; 1.3).

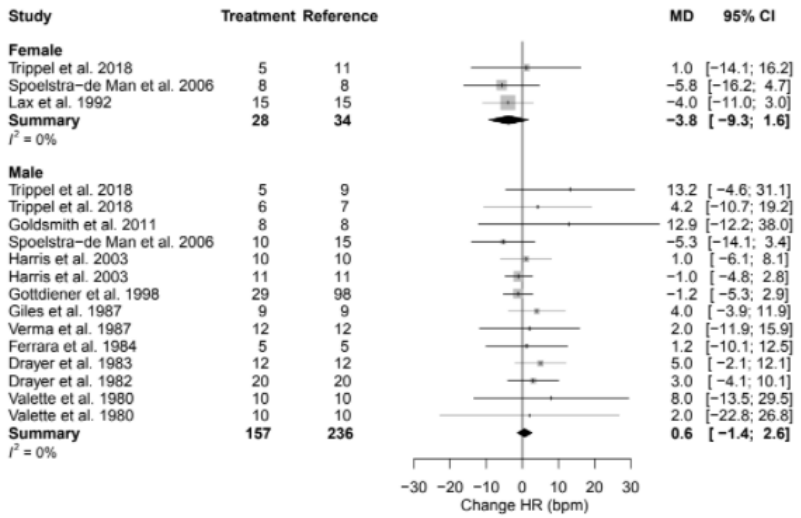


Figure 10 Forest plot of heart rate (HR) change in beats per minute (BPM) after diuretic use compared to baseline for females and males. MD = mean difference

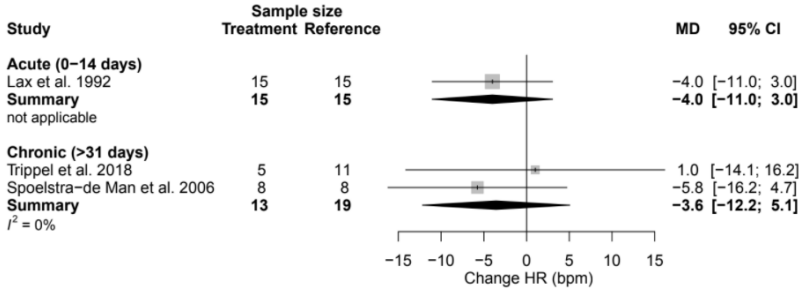


Figure 11 Forest plot of heart rate (HR) change in beats per minute (BPM) after acute, sub-acute and chronic diuretic use compared to baseline for females. MD = mean difference

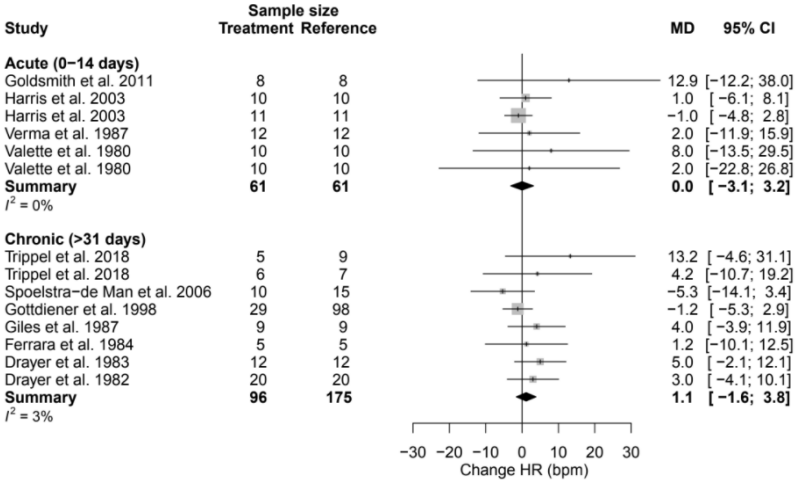


Figure 12 Forest plot of heart rate (HR) change in beats per minute (BPM) after acute, sub-acute and chronic diuretic use compared to baseline for males. MD = mean difference

CARDIAC OUTPUT

The mean cardiac output (CO) in the studies population was 4.3 L/min (95% CI, 3.9; 4.8) in females (n=18) and 4.8 L/min (95% CI, 3.8; 5.8) in males (n=33) at baseline (p = 0.3885). Diuretic effect on CO was analyzed based on three male and two female studies. Although CO decreased 0.7 L/min (95% CI, -1.2; -0.2)(-15.3% (95% CI, -27.0; -3.6)) after diuretic treatment in females, it did not have a

statistically significant effect in males (CO, -0.1 L/min (95% CI, -0.8; 0.6))(-2.3% (95% CI, -16.7; 12.0)) (Table 3, Figure 13). No sex difference in CO was observed (p = 0.2000). The mean difference for CO by treatment duration is reported in Table 4. Due to the small number of included articles, it is hard to draw solid conclusions on the effect of treatment duration on CO (Figures 14, 15). Clinical and methodological heterogeneity did not affect the change in CO (Table 5). Egger's regression test for funnel plot asymmetry was not statistically significant for males (p = 0.2634) and could not be performed for females due to the small number of included studies.

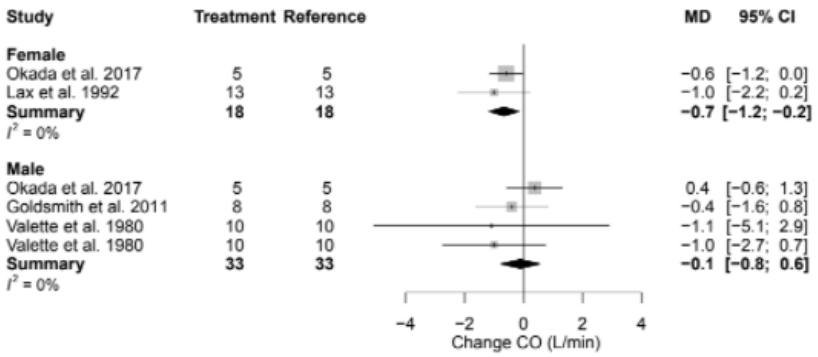


Figure 13 Forest plot of cardiac output (CO) change in L/min after diuretic use compared to baseline for females and males. MD = mean difference

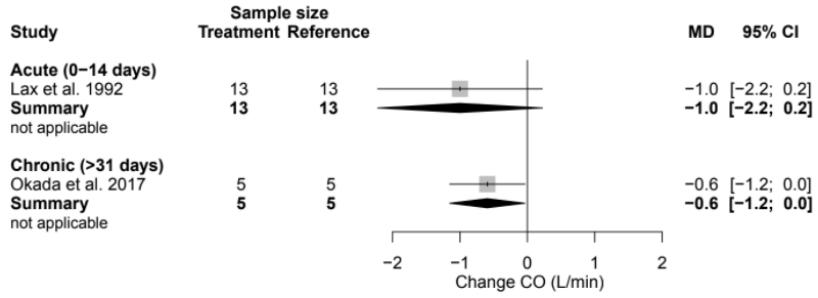


Figure 14 Forest plot of cardiac output (CO) change in L/min after acute, sub-acute and chronic diuretic use compared to baseline for females. MD = mean difference

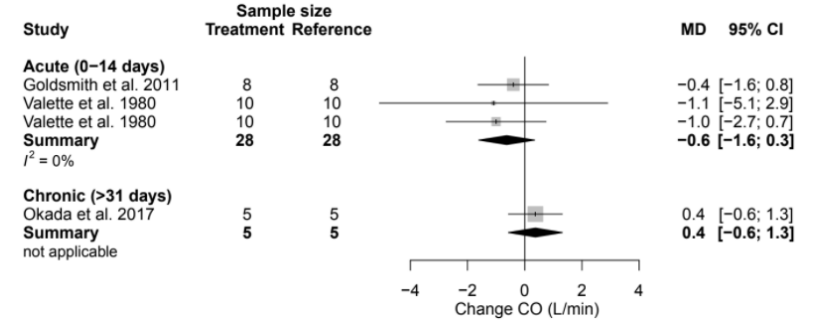


Figure 15 Forest plot of cardiac output (CO) change in L/min after acute, sub-acute and chronic diuretic use compared to baseline for males. MD = mean difference

LEFT VENTRICULAR EJECTION FRACTION

The mean left ventricular ejection fraction (LVEF) in the studies population was 62.0% (95 CI%, 57.7; 66.3) in females (n=10) and 61.2% (95% CI, 56.8; 65.7) in males (n=15) at baseline (p = 0.8105). The change in LVEF in females was based on only one study. In this study measuring a chronic effect of diuretic use, LVEF remained unaltered (1.0% (95% CI, -5.1; 7.1)(1.6% (95% CI, -8.3; 11.5)) (Table 3, Figure 16). The effect in males was based on two studies on chronic diuretic use, which also showed an insignificant change (1.4% (95% CI, -4.7; 7.4)(2.2% (95% CI, -7.6; 12.1)). The effect on LVEF from baseline was not different between sexes (p = 0.9314). Meta-regression analysis and Egger's regression test for funnel plot asymmetry could not be performed because of the small number of included studies.

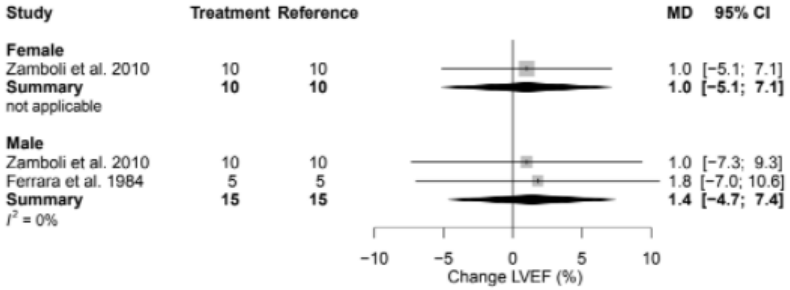


Figure 16 Forest plot of left ventricular ejection fraction (LVEF) change in % after diuretic use compared to baseline for females and males. MD = mean difference

LEFT VENTRICULAR MASS

The mean left ventricular mass (LVM) in the studies population was 193.9 g (95% CI, 177.3; 210.6) in females (n=34) and 262.0 g (95% CI, 200.0; 324.0) in males (n=141) at baseline (p = 0.0375). Data of two studies on chronic diuretic use showed that left ventricular mass (LVM) did not change in females (-1.6 g (95% CI, -24.3; 21.0)(-0.8% (95% CI, -12.5; 10.8)) (Table 3, Figure 17). In males, chronic diuretic treatment lowered LVM with 25.5 g (95% CI, -44.4; -6.6)(-9.4% (95% CI, -16.4; -2.4)). No statistically significant sex difference was observed (p = 0.1131). Clinical and methodological heterogeneity did not affect the change in LVM (Table 5). Egger's regression test for funnel plot asymmetry was not statistically significant for males (p = 0.9705) and could not be performed for females due to the small amount of included studies.

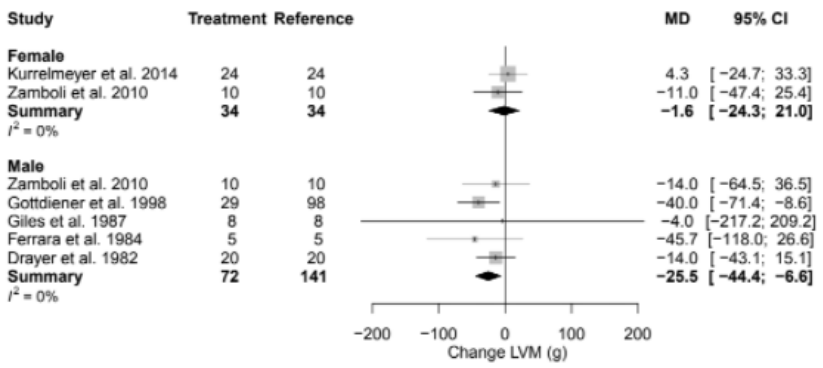


Figure 17 Forest plot of left ventricular mass (LVM) change in g after diuretic use compared to baseline for females and males. MD = mean difference

Discussion

In this systematic review and meta-analysis, we observed that diuretics lower blood pressure significantly in both sexes but more pronounced in females and especially when used chronically. Diuretic treatment significantly decreased CO in females and LVM in males, whereas it did not change HR and LVEF in both sexes. However, over a period encompassing 75 years only 18 studies were suitable to be used to stratify data based on sex, in which a very small minority concerned females.

Diuretics as monotherapy are especially effective in lowering systolic blood pressure[40], a finding in line with our observation. In the acute phase of diuretic administration, a blood pressure decrease is caused by a depletion in blood and plasma volume paralleled by a decreased CO and an increased total peripheral resistance. These systemic hemodynamic effects change after long-term diuretic administration as blood and plasma volume either remains reduced or normalizes, whereas total peripheral resistance decreases thereby maintaining a reduced blood pressure compared to pre-treatment levels[41]. Most studies included in this meta-analysis evaluated chronic treatment effects of diuretics. Based on the pharmacological mechanism of diuretics, only a change in CO in the acute phase is expected next to a decrease in blood pressure. However, as this meta-analysis could include only few studies measuring CO after acute treatment with diuretics, no decrease in CO was found.

Next to these systemic hemodynamic effects, diuretics also manifest renal hemodynamic effects which affect blood pressure. Most studies evaluating these renal hemodynamic effects only studied the acute effects of diuretics in animal models. On the one hand, diuretic agents primarily working on the distal convoluted tubule and collecting duct did not affect renal blood or plasma flow, glomerular filtration rate (GFR) or filtration fraction. On the other hand, the carbonic anhydrase inhibitors inhibiting transport in the proximal nephron were shown to reduce renal blood flow and reduce GFR. Some diuretic groups inhibiting transport in the loop of Henle, like sulfonamide derivates, ethacrynic acid and mannitol, were shown to increase renal blood flow, while exhibiting no effect on GFR and no effect or a decreased effect on filtration fraction. These intrarenal hemodynamic changes affect renal excretion by modulating the reabsorptive rate of the tubular system. A second mechanism by which renal excretion can be altered is based on a diminished filtered load of sodium when the GFR reduces[41,42].

We observed a greater effect on lowering systolic blood pressure in females. Since in the general practice females are more likely to be treated with diuretics than males[43,44], it may be that most females receive an effective (systolic) blood pressure lowering treatment. Considering the decreased renal calcium excretion that usually accompany diuretic usage, some even argue that it might be of additional benefit with respect to bone density and fracture risk as hypertension is commonly used by postmenopausal females[44]. Pharmacogenetic factors involved in the pharmacological response to therapy might also differ between females and males and might explain why diuretics appear to be

more effective in females. Schwartz *et al.*[45] suggested that the blood pressure response to hydrochlorothiazide is possibly based on a sex-specific interaction with the angiotensin I-converting enzyme (ACE) gene, although they could not explain this phenomenon only based on ACE activity.

Despite good pharmacological effects of diuretics in females, it is also known that they experience more often adverse events compared to males, a phenomenon which could not be explained by a higher prescription rate in females[46]. A study by Werner *et al.*[47] found that female sex was a predictor of the pharmacokinetics of the loop diuretic torasemide. Moreover, an animal study showed that renal clearance of the loop diuretic furosemide was significantly less in female than in male rats[48]. Another animal study found that both furosemide and torasemide caused more effective diuresis, natriuresis, and kaliuresis in female than in male rats[13]. Hyponatremia and hypokalemia were more often reported in female patients. Nevertheless, clinical trials did not find a higher incidence of severe cardiac arrhythmias, a serious consequence of electrolyte disturbances, in females [49]. The pharmacokinetics of thiazide diuretics appear to be partly influenced by sex and sex hormones which regulate the density of renal thiazide diuretic receptors[50].

Although not the aim of this systematic review, another important finding deserves attention and awareness. Females are underrepresented in clinical trials regarding diuretics, and sex-stratified analysis are rarely reported articles. And since we observed differences in circulatory response to diuretics between females and males, these findings call for a more sex-stratified approach in future studies. A scoping review on participation of females in clinical trials on antihypertensive drugs during the past decades showed that females are still underrepresented in these studies. Although an increase in inclusion of females in clinical trials was found, between 2011 and 2020 still only one third of the included participated were female[51]. Two systematic reviews and meta-analyses on sex differences in effects of beta-blockers[52] and calcium channel blockers [53] also reported on this topic and stressed the need for more sex-stratified data reporting in clinical studies.

Our meta-analysis showed a greater effect in blood pressure decrease after long-term diuretic use, defined as more than 30 days. It appears that the mechanism by which diuretics can decrease blood pressure differs in short-term and long-term use. In the initial weeks after start of diuretic treatment, a decrease in plasma volume, venous return and cardiac output relates to a decrease in blood pressure. In patients with long-term diuretic treatment a decrease in arterial resistance is mainly responsible for blood pressure decrease, whereas cardiac output and plasma volume nearly return to pre-treatment values[9].

To our knowledge, the current study is the first to evaluate the sex differences in effect of diuretics. Despite, several shortcomings at the study and outcome level need to be reported. First, some patients in the included studies received comedication for underlying suffering, which might have biased the calculated intervention effect. But since baseline medication was reported to be unaltered before and after diuretic treatment,

we consider the change within individuals to be the resultant of the used diuretic compound. Second, this meta-analysis included more studies which only studied male subjects. As a result, the total amount of males studied in this meta-analysis (n = 6,810) was not in proportion to the total amount of females studied (n = 68). Moreover, the vast majority of the articles screened for this systemic review did not report sex-stratified data for the variables of interest. Sex-specific data was requested via email, but the overall response rate was low. As a result, many potentially suitable articles had to be excluded from this meta-analysis. Because studies who included both sexes did not separate the outcomes for males and females, the majority of the included studies only investigated one sex. Studies focusing on males were more available and met the inclusion criteria for this systematic review more often. This was especially the case for the oldest studies in this systematic review. It may be that the old paradigm that CVD was viewed upon as a men's disease, led to the situation that, most and mainly older studies, included only male participants in their clinical studies [54]. Third, one third of the articles included in this systematic review were qualified as high risk of bias by RoB2 tool. Nonetheless, the effects of RoB2 assessed quality, did not show significant effects on outcome as evaluated by meta-regression analysis. Finally, the presence of heterogeneity might affect interpretation of meta-analysis outcomes. Although we observed some heterogeneity in some variables, which is always prerequisite for careful interpretation of findings, our additional meta-regression to detect sources of heterogeneity may help to value findings.

Conclusion and Recommendations

This systematic review and meta-analysis showed that diuretics substantially lower blood pressure, especially when used more than a month. Sex differences in reached response may exist not only in pressure response but also cardiac remodeling and systolic function. Given the large difference in studied females as compared to males, future studies should aim for a more sex-stratified approach.

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.

Funding:

None.

Acknowledgements:

The authors extensively thank the biomedical sciences students (Lieke Knapen, Rosamel Abeka, Thom Knoben, Samantha Schwengle, Ryan van den Akker) and medical students of the Maastricht University honors program (Cédric Dikovec, Jan Wiesenberg, Mohamad Almutairi) involved in data extraction and risk of bias assessment.

Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

Author's contribution

Esmée Vaes, Nicks Wilmes, Daniek Meijs, Sophie Laven, Maud Vesseur, Zenab Mohseni-Alsalhi, Eveline van Luik, Cédric Dikovec, Jan Wiesenberg and Mohamad Almutairi performed the search, study selection, and data extraction. Sander de Haas analyzed the data. Esmée Vaes wrote the initial draft of the paper, revised the paper and finalized the manuscript. Marc Spaanderman, Chahinda Ghossein-Doha initiated the project, developed the idea and coordinated the writing process. Esmée Vaes, Marc Spaanderman, Chahinda Ghossein-Doha wrote the paper and critically reviewed the content.

References:

1. Organization WH. Cardiovascular diseases (CVDs). Webpage. 20 September, 2020. Updated 17 May 2017. https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

2. Di Giosia P, Passacquale G, Petrarca M, Giorgini P, Marra AM, Ferro A. Gender differences in cardiovascular prophylaxis: Focus on antiplatelet treatment. *Pharmacological Research*. 2017/05/01/ 2017;119:36-47. doi: https://doi.org/10.1016/j.phrs.2017.01.025

3. MayoClinic. Heart disease in women: Understand symptoms and risk factors. Webpage. 20 September, 2020. Updated 4 October 2019. https://www.mayoclinic.org/diseases-conditions/heart-disease/in-depth/heart-disease/art-20046167

4. Appelman Y, van Rijn BB, ten Haaf ME, Boersma E, Peters SAE. Sex differences in cardiovascular risk factors and disease prevention. *Atherosclerosis*. 2015/07/01/ 2015;241(1):211-218. doi:https://doi.org/10.1016/j.atherosclerosis.2015.01.027

5. Gao Z, Chen Z, Sun A, Deng X. Gender differences in cardiovascular disease. *Medicine in Novel Technology and Devices*. 2019/12/01/ 2019;4:100025. doi:https://doi.org/10.1016/j.medntd.2019.100025

6. Saklayen MG, Deshpande NV. Timeline of History of Hypertension Treatment. *Front Cardiovasc Med*. 2016;3:3. doi:10.3389/fcvm.2016.00003

7. Klabunde R. *Cardiovascular physiology concepts*. Lippincott Williams & Wilkins; 2011.

8. Kompas F. Diuretica. Web page. 1 December, 2020. Accessed 30 January, 2013. https://nvkfb.nl/wp-content/uploads/2019/03/FK-Inleidende-tekst-Diuretica.pdf

9. Ernst ME, Mann SJ. Diuretics in the treatment of hypertension. *Semin Nephrol*. Nov 2011;31(6):495-502. doi:10.1016/j.semnephrol.2011.09.004

10. Franson KL, Kuk JM, Lam NP, Lau AH. Gender effect on diuretic response to hydrochlorothiazide and furosemide. *Int J Clin Pharmacol Ther*. Mar 1996;34(3):101-5.

11. Tamargo J, Rosano G, Walther T, et al. Gender differences in the effects of cardiovascular drugs. *Eur Heart J Cardiovasc Pharmacother*. Jul 1 2017;3(3):163-182. doi:10.1093/ehjcvp/pvw042

12. Hendriksen LC, van der Linden PD, Lagro-Janssen ALM, et al. Sex differences associated with adverse drug reactions resulting in hospital admissions. *Biol Sex Differ*. May 3 2021;12(1):34. doi:10.1186/s13293-021-00377-0

13. Brandoni A, Villar SR, Torres AM. Gender-related differences in the pharmacodynamics of furosemide in rats. *Pharmacology*. Feb 2004;70(2):107-12. doi:10.1159/000074675

14. Chen JM, Heran BS, Wright JM. Blood pressure lowering efficacy of diuretics as second-line therapy for primary hypertension. *Cochrane Database Syst Rev*. Oct 7 2009;(4):Cd007187. doi:10.1002/14651858.CD007187.pub2

15. Musini VM, Nazer M, Bassett K, Wright JM. Blood pressure-lowering efficacy of monotherapy with thiazide diuretics for primary hypertension. *Cochrane Database Syst Rev*. May 29 2014;(5):Cd003824. doi:10.1002/14651858.CD003824.pub2

16. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. Webpage. Cochrane Methods Bias. 16 December, 2020. https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

17. Higgins JT, J. Cochrane Handbook for Systematic Reviews of Interventions. 2020:chap 6.

18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. Sep 1986;7(3):177-88. doi:10.1016/0197-2456(86)90046-2

19. Deeks JJ, Higgins JPT, DG. A. Chapter 10: Analysing data and untertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, et al, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane; 2020:chap Chapter 10.

20. Schwarzer G. meta: An R package for meta-analysis. *R news*. 2007;7(3):40-45.

21. Team RC. R: A Language and Environment for Statistical Computing. *R Foundation for Statistical Computing*. Vienna, 2016;

22. Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. *Hypertension*. Apr 2011;57(4):689-94. doi:10.1161/hypertensionaha.110.161505

23. Okada Y, Shibata S, Fujimoto N, Best SA, Levine BD, Fu Q. Long-term effects of a renin inhibitor versus a thiazide diuretic on arterial stiffness and left ventricular diastolic function in elderly hypertensive patients. *Am J Physiol Regul Integr Comp Physiol*. Oct 1 2017;313(4):R400-r409. doi:10.1152/ajpregu.00125.2017

24. Spoelstra-de Man AM, van Ittersum FJ, Schram MT, et al. Aggressive antihypertensive strategies based on hydrochlorothiazide, candesartan or lisinopril decrease left ventricular mass and improve arterial compliance in patients with type II diabetes mellitus and hypertension. *J Hum Hypertens*. Aug 2006;20(8):599-611. doi:10.1038/sj.jhh.1002025

25. Gottdiener JS, Reda DJ, Williams DW, Materson BJ, Cushman W, Anderson RJ. Effect of single-drug therapy on reduction of left atrial size in mild to moderate hypertension: comparison of six antihypertensive agents. *Circulation*. Jul 14 1998;98(2):140-8. doi:10.1161/01.cir.98.2.140

26. Giles TD, Sander GE, Roffidal LC, Thomas MG, Given MB, Quiroz AC. Comparison of nitrendipine and hydrochlorothiazide for systemic hypertension. *Am J Cardiol*. Jul 1 1987;60(1):103-6. doi:10.1016/0002-9149(87)90994-5

27. Drayer JI, Weber MA, Gardin JM, Lipson JL. Effect of long-term antihypertensive therapy on cardiac anatomy in patients with essential hypertension. *Am J Med*. Sep 26 1983;75(3a):116-20. doi:10.1016/0002-9343(83)90128-6

28. Drayer JI, Gardin JM, Weber MA, Aronow WS. Changes in ventricular septal thickness during diuretic therapy. *Clin Pharmacol Ther*. Sep 1982;32(3):283-8. doi:10.1038/clpt.1982.161

29. Materson BJ, Michael UF, Oster JR, Perez-Stable EC. Antihypertensive effects of oxprenolol and propranolol. *Clin Pharmacol Ther*. Aug 1976;20(2):142-51. doi:10.1002/cpt1976202142

30. Solini A, Seghieri M, Giannini L, et al. The Effects of Dapagliflozin on Systemic and Renal Vascular Function Display an Epigenetic Signature. *J Clin Endocrinol Metab*. Oct 1 2019;104(10):4253-4263. doi:10.1210/jc.2019-00706

31. Ferrara LA, de Simone G, Pasanisi F, Mancini M, Mancini M. Left ventricular mass reduction during salt depletion in arterial hypertension. *Hypertension*. Sep-Oct 1984;6 (5):755-9. doi:10.1161/01.hyp.6.5.755

32. Zamboli P, De Nicola L, Minutolo R, et al. Effect of furosemide on left ventricular mass in non-dialysis chronic kidney disease patients: a randomized controlled trial. *Nephrol Dial Transplant*. May 2011;26(5):1575-83. doi:10. 1093/ndt/gfq565

33. Lax D, Eicher M, Goldberg SJ. Mild dehydration induces echocardiographic signs of mitral valve prolapse in healthy females with prior normal cardiac findings. *Am Heart J*. Dec 1992;124(6):1533-40. doi:10.1016/000 2-8703(92)90068-7

34. Verma SP, Silke B, Hussain M, et al. First-line treatment of left ventricular failure complicating acute myocardial infarction: a randomised evaluation of immediate effects of diuretic, venodilator, arteriodilator, and positive inotropic drugs on left ventricular function. *J Cardiovasc Pharmacol*. Jul 1987;10 (1):38-46. doi:10.1097/00005344-198707000-00006

35. Valette H, Hebert JL, Raffestin B, Lockhart A, Apoil E. Comparison of hemodynamic effects of furosemide and piretanide in normovolemic patients. *J Cardiovasc Pharmacol*. 1980;2(2):103-11. doi:10.1097/00 005344-198003000-00002

36. Goldsmith SR, Gilbertson DT, Mackedanz SA, Swan SK. Renal effects of conivaptan, furosemide, and the combination in patients with chronic heart failure. *J Card Fail*. Dec 2011;17(12):982-9. doi:10.1016/j.cardfail.2011.08.012

37. Trippel TD, Van Linthout S, Westermann D, et al. Investigating a biomarker-driven approach to target collagen turnover in diabetic heart failure with preserved ejection fraction patients. Effect of torasemide versus furosemide on serum C-terminal propeptide of procollagen type I (DROP-PIP trial). *Eur J Heart Fail*. Mar 2018;20(3):460-470. doi:10.1 002/ejhf.960

38. Kurrelmeyer KM, Ashton Y, Xu J, Nagueh SF, Torre-Amione G, Deswal A. Effects of spironolactone treatment in elderly women with heart failure and preserved left ventricular ejection fraction. *J Card Fail*. Aug 2014;20(8):560-8. doi:10.1016/j.cardfail.2014.05.010

39. Harris SK, Petrella RJ, Overend TJ, Paterson DH, Cunningham DA. Short-term training effects on left ventricular diastolic function and oxygen uptake in older and younger men. *Clin J Sport Med*. Jul 2003;13(4):245-51. doi:10.1097/00042752-20 0307000-00009

40. Musini VM, Nazer M, Bassett K, Wright JM. Blood pressure-lowering efficacy of monotherapy with thiazide diuretics for primary hypertension. *Cochrane Database of Systematic Reviews*. 2014;(5)

41. Puschett J. The hemodynamic effects of diuretics. *Nefrologia*. 1990;X(1)

42. Ray EC, Boyd-Shiwarski CR, Kleyman TR. Why Diuretics Fail Failing Hearts. *Journal of the American Society of Nephrology*. 2017;2 8(11):3137-3138. doi:10.1681/asn.2017070797

43. Klungel OH, de Boer A, Paes AH, Seidell JC, Bakker A. Sex differences in the pharmacological treatment of hypertension: a review of population-based studies. *J*

Hypertens. Jun 1997;15(6):591-600. doi:10.1097/00004872-199715060-00004

44. Thoenes M, Neuberger H, Volpe M, Khan B, Kirch W, Böhm M. Antihypertensive drug therapy and blood pressure control in men and women: an international perspective. *Journal of human hypertension*. 2010;24(5):336-344.

45. Schwartz GL, Turner ST, Chapman AB, Boerwinkle E. Interacting effects of gender and genotype on blood pressure response to hydrochlorothiazide. *Kidney international*. 2002;62(5):1718-1723.

46. Werner D, Werner U, Meybaum A, et al. Determinants of steady-state torasemide pharmacokinetics: impact of pharmacogenetic factors, gender and angiotensin II receptor blockers. *Clin Pharmacokinet*. 2008;47(5):323-32. doi:10.21 65/00003088-200847050-00003

47. Werner U, Werner D, Heinbüchner S, et al. Gender is an important determinant of the disposition of the loop diuretic torasemide. *J Clin Pharmacol*. Feb 2010;50(2):160-8. doi:10.1177/0091270009337514

48. Cerrutti JA, Quaglia NB, Brandoni A, Torres AM. Effects of gender on the pharmacokinetics of drugs secreted by the renal organic anions transport systems in the rat. *Pharmacol Res*. Feb 2002;45(2):107-12. doi:10.1006/phrs.2001.0912

49. *Sex and Gender Differences in Pharmacology*. 1 ed. Handbook of Experimental Pharmacology. Springer Berlin, Heidelberg; 602.

50. Chen Z, Vaughn DA, Fanestil DD. Influence of gender on renal thiazide diuretic receptor density and response. *Journal of the American Society of Nephrology*. 1994;5(4):1112-1119. doi:10.1681/asn.V541112

51. Mohseni-Alsalhi Z, Vesseur MAM, Wilmes N, et al. The Representation of Females in Studies on Antihypertensive Medication over the Years: A Scoping Review. *Biomedicines*. May 12 2023;11(5)doi:10.3390/biomedicines11051435

52. Wilmes N, van Luik EM, Vaes EWP, et al. Exploring Sex Differences of Beta-Blockers in the Treatment of Hypertension: A Systematic Review and Meta-Analysis. *Biomedicines*. May 22 2023;11(5)doi:10.3390/biomedicines11051494

53. van Luik EM, Vaes EWP, Vesseur MAM, et al. Sex Differences in the Anti-Hypertensive Effect of Calcium-Channel Blockers: A Systematic Review and Meta-Analysis. *Biomedicines*. Jun 2 2023;11(6)doi:10.3390/biomedicines11061622

54. Federman D, Faden R, Mastroianni AC. *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies, Volume 1*. vol 1. National Academies Press; 1994.

55. Hydrochloorthiazide. Farmacotherapeutisch Kompas. 19 January, 2021. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/h/hydrochloorthiazide

56. furosemide - Drug Summary. Web page. Prescriber's Digital Reference. 19 January, 2021. https://www.pdr.net/drug-summary/Furosemide-Injection-furosemide-1557

57. Torsemide Dosage. Web page. 19 January, 2021. Updated March 2, 2020. https://www.drugs.com/dosage/torsemide.html#

58. Spironolactone: Drug information. Web page. UpToDate. 19 January, 2021. https://www-uptodate-com.ezproxy.ub.unimaas.nl/contents/spironolactone-drug-information?sectionName=Adult&topicId=9943&search=spironolacton&usage_type=pane

l&anchor=F222866&source=panel_search_result&selectedTitle=1~148&kp_tab=drug_general&display_rank=1

59. Chloortalidon. Web page. Farmacotherapeutisch Kompas. 19 January, 2021. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/c/chloortalidon

60. Piretanide. Web page. National Center for Advancing Translational Sciences. 19 January, 2021. https://drugs.ncats.io/drug/DQ6KK6GV93

Supplements

Table S1 PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pages 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5, table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 7

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 7-8, table 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pages 7-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pages 7-8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9, figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9
Study characteristics	17	Cite each included study and present its characteristics.	Pages 9-10, table 2
Risk of bias in	18	Present assessments of risk of bias for each included study.	Page 10, table 3

Section and Topic	Item #	Checklist item	Location where item is reported
studies			
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pages 10-13
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pages 10-13
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pages 10-13
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pages 10-13
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pages 10-13
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Table 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pages 10-13
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 13-15
	23b	Discuss any limitations of the evidence included in the review.	Pages 15-16
	23c	Discuss any limitations of the review processes used.	Pages 15-16
	23d	Discuss implications of the results for practice, policy, and future research.	Page 16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 17
Competing interests	26	Declare any competing interests of review authors.	Page 17

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 5

Table S2 Characteristics of studies

Table S2 Characteristics of studies

Study	Patient	Ethni-city	Diuretic treatment (administration)	Mean dose (mg/day)	% max dose*	Subjects diuretics (n)			Control group**	Controls (n)			Age (years + SD)	Intervention duration (days)	Study design	Extracted variables	Method of measurement
						Total	M	F		Total	M	F					
Solini (2019) [30]	T2D, HTN	-	Hydrochlorothiazide (oral)	12.5	25	20	14	6	Dapagli-flozin	20	12	8	62 (8)	28	RCT	SBP, DBP	Arterial tonometry
Trippel (2018) [37]	T2D, HFpEF	W	Furosemide (oral) Torasemide (oral)	20 5	3 50	18 17	7 13	11 4	-	-	-	-	68.7 (8.1)	270	RCT	SBP, DBP, HR	Sphygmo-manometry, ECG
Okada (2017) [23]	HTN	-	Hydrochlorothiazide (oral)	20	40	10	5	5	Aliskiren	11	5	6	67 (14)	183	RCT	SBP, DBP, CO	Sphygmo-manometry, acetylene rebreathing method
Kurrelmeyer (2014) [38]	HFpEF	-	Spironolactone (oral)	25	30	24	0	24	Placebo	24	0	24	71.4 (5.4)	183	RCT	LVM	Echo
Dorsch (2011) [22]	At risk for death from CHD	W, B	Chlorthalidone (oral) Hydrochlorothiazide (oral)	73.9 64.2	150 130	2392 4049	2392 4049	0 0	-	-	-	-	46.8 (5.8)	2555	Retrospec-tive cohort	SBP	Sphygmo-manometry
Goldsmith (2011) [36]	HFrEF	W, B	Furosemide (iv)	77.5	100	8	8	0	Conivaptan	8	8	0	51 (5.9)	3	RCT, cross-over	SBP, DBP, HR, CO	Sphygmo-manometry, impedance cardiography
Zambol i (2010) [32]	non-dialysis CKD	-	Furosemide (oral)	65	10	20	10	10	Non-diuretic	20	12	8	73.6 (7.5)	365	RCT	SBP, DBP, LVEF, LVM	Sphygmo-manometry, echo

Spoelstra-de Man (2006) [24]	T2D, HTN	W	Hydrochlorothiazide (oral)	25	50	24	16	8	Candesartan or lisinopril	46	27	19	62 (7)	365	RCT	SBP, DBP, HR	Sphygmomanometry
Harris (2003) [39]	Healthy	-	Spironolactone (oral)	100	100	21	21	0	Exercise or combination	21	21	0	47 (23)	7	RCT, cross-over	HR	ECG

Study	Patient	Ethnicity	Diuretic treatment (administration)	Mean dose (mg/day)	% max dose*	Subjects diuretics (n)			Control group**	Controls (n)			Age (years + SD)	Intervention duration (days)	Study design	Extracted variables	Method of measurement
						Total	M	F		Total	M	F					
Gottdiener (1998) [25]	HTN	W, B	Hydrochlorothiazide (oral)	31.3	63	188	188	0	Atenolol, captopril, clonidine, diltiazem, prazosin	917	917	0	58.8 (10)	730	RCT	DBP	Sphygmomanometry
Lax (1992) [33]	Healthy	-	Furosemide (oral)	20	3	15	0	15	Placebo	15	0	15	27 (1)	2	RCT, cross-over	DBP, HR, CO	
Giles (1987) [26]	HTN	W, B	Hydrochlorothiazide (oral)	50	100	9	9	0	Nitrendipine	9	9	0	65.5 (8)	56	RCT	SBP, DBP, HR, LVM	Sphygmomanometry, echo
Verma (1987) [34]	AMI	-	Frusemide (iv)	84	105	12	12	0	Isosorbide dinitrate, hydralazine, prenalterol	36	36	0	58.3 (***)	0.063	RCT	HR	ECG
Ferrara (1984) [31]	HTN	-	Chlorthalidone (oral)	25	50	5	5	0	Low salt intake	5	5	0	39.7 (7)	84	RCT, cross-over	SBP, DBP, HR, LVEF, LVM	Sphygmomanometry, echo
Drayer (1983) [27]	HTN	W, B	Hydrochlorothiazide (oral)	95.8	192	12	12	0	Alpha-methyldopa (in addition to diuretic after 42 days)	12	12	0	59.2 (13)	267	Prospective cohort	SBP, DBP, HR	Sphygmomanometry
Drayer (1982) [28]	HTN	W, B	Hydrochlorothiazide (oral)	100	200	20	20	0	-	-	-	-	54.8 (2)	42	Prospective cohort	SBP, DBP, HR, LVM	Sphygmomanometry, echo

Valette (1980) [35]	Post-MI	-	Furosemide (iv)	40	50	10	10	0	-	-	-	-	51.2 (***)	0.031	RCT	HR, CO	Catheteri-sation
			Piretanide (iv)	12	67	10	10	0									

Study	Patient	Ethni -city	Diuretic treatment (administration)	Mean dose (mg/day)	% max dose*	Subjects diuretics (n)			Control group**	Controls (n)			Age (years + SD)	Intervention duration (days)	Study design	Extracted variables	Method of measurem ent
						Total	M	F		Total	M	F					
Materson (1976) [29]	HTN	W, B	Hydrochlorothiazide (oral)	50	100	15	15	0	Oxprenolol or propranolol (in addition to diuretic after 21 days)	24	24	0	52 (***)	120	RCT	SBP, DBP	Sphygmo-manometry
			Hydrochlorothiazide (oral)	100	200	9	9	0									