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**Document status and date:**
Published: 01/02/2019

**DOI:**
10.1097/HJH.0000000000001918

**Document Version:**
Publisher's PDF, also known as Version of record

**Document license:**
Taverne

**Please check the document version of this publication:**

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**Link to publication**

# Review

# Do treatment-induced changes in arterial stiffness affect left ventricular structure? A meta-analysis

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**See editorial comment on page 280**

**Background:** Vascular research demonstrated that pulse wave velocity (PWV), a measure of arterial stiffness, is inherently blood pressure dependent. Considering the hypothesized pathophysiological chain of increased arterial stiffness leading to increased blood pressure load with consequent left ventricular hypertrophy (LVH) development, we conducted a systematic review of antihypertensive and lifestyle intervention studies to determine the association between, on the one hand, changes in arterial stiffness and blood pressure, and, on the other hand, changes in left ventricular mass (LVM).

**Methods:** Using PubMed, EMBASE, Cochrane and Web of Science, we identified 23 studies, containing 2573 patients. Studies reported changes in arterial stiffness (assessed by means of PWV), SBP, DBP and LVM index (LVMI), respectively.

**Results:** Statistically significant reductions in SBP, PWV and LVMI were reported in 16, 14 and 20 studies, respectively. Pooled analysis of studies showed that the proportion in SBP reduction did not correlate significantly to the proportion in reductions of the other two variables. On the contrary, we found a significant positive correlation ($r = 0.61$, $P = 0.003$) between arterial stiffness and reduction of LVM, expressed as a relevant reduction in LVMI of 6.9 g/m$^2$ per 1.0 m/s reduction in PWV.

**Conclusion:** Our findings provide evidence that a decrease in arterial stiffness is associated with reduction of LVM. To investigate whether there exists a causal relation between LVH due to arterial stiffness increases and in turn blood pressure load increases, future studies should strive for a multiple follow-up design and use of blood pressure independent or corrected stiffness indices.

**Keywords:** aging, diastolic dysfunction, hypertensive heart disease, left ventricular hypertrophy, ventricular-vascular coupling

**Abbreviations:** $A_0$, diastolic cross-sectional lumen area; CC, compliance; CI, confidence interval; LVM, left ventricular mass; LVMI, left ventricular mass index; PWV, pulse wave velocity; $\rho$, blood density

## INTRODUCTION

Currently, cardiovascular disease (CVD) is the number one killer of humans worldwide, responsible for 17.7 million deaths (approximately 30% of all deaths) each year [1]. In the elderly, CVD accounts for even more than 80% of all deaths [2]. High arterial blood pressure is a key determinant of CVD [3] and is the leading attributable factor for developing heart failure [4]. Elevated isolated SBP is becoming increasingly relevant in the ageing population, as 60% of people aged 60 years or older have elevated SBP (>140 mmHg) [5].

The (age-related) stiffening of arteries has been identified as a key determinant and precursor of elevated SBP [6–8]. The main contributors to elevated SBP are believed to be decreased (central) arterial compliance and increased systolic wave reflection (i.e. earlier arrival of reflected pressure wave) [7]. Increased myocardial afterload due to elevated SBP affects the way the left ventricle (LV) adapts and becomes hypertrophic [9]. Recently, the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines for the management of hypertension have emphasized the importance of increased arterial stiffness [assessed as pulse wave velocity (PWV)] and left ventricular hypertrophy (LVH) [assessed as left ventricular mass index (LVMI)] in determining the overall cardiovascular risk [10].

A pattern of increased arterial stiffness, high blood pressure and LVH is frequently observed in smaller observational, cross-sectional studies [11–13]. Due to design and study size, such studies are seriously limited in identifying causality. Furthermore, arterial stiffness measurements are inherently blood pressure dependent [14], complicating the causative interpretation of observed changes in both arterial stiffness and left ventricular structure and function.

Considering the current pathophysiological paradigm linking arterial stiffening, elevation of SBP and development of LVH/failure [15], our aim was to review the available randomized control trials (RCTs) and cohort studies, reporting intervention-induced changes in blood pressure,

arterial stiffness and left ventricular structure/function as primary outcomes. We evaluated whether intervention-induced changes in arterial stiffness correlated with improvement in left ventricular structure and function. In our meta-analysis, we included the orders of magnitude of changes in PWV and of changes in LVM, in relation to changes in SBP and DBP.

## MATERIALS AND METHODS

### Protocol and registration
In this study, we applied the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for studies evaluating medical interventions [16].

### Search strategy and study selection
We extensively searched the PubMed, EMBASE, Cochrane and Web of Science databases using the following search strategy: (((((((((((Heart Failure, Diastolic[MeSH Terms]) OR Heart Failure, Diastolic) OR diastolic dysfunction) OR isolated systolic hypertension) OR pulse pressure) OR Blood pressure[MeSH Terms])) AND (((((((Hypertrophy, Left Ventricular[MeSH Terms]) OR Hypertrophy, Left Ventricular) OR left ventricle hypertrophy) OR cardiac hypertrophy) OR cardiomegaly[MeSH Terms]) OR cardiomegaly)) AND (((((((blood pressure) OR blood pressure[MeSH Terms]) OR hypertension[MeSH Terms]) OR high blood pressure) OR hypertension)) AND (((((((arterial stiffness) OR vascular stiffness[MeSH Terms]) OR vascular stiffness) OR pulse wave velocity) OR pulse wave analysis[MeSH Terms]) OR pulse wave analysis) OR distensibility))))) AND ((((physical activity*) OR motor activity) OR Motor activity[MeSH Terms]) OR ((((((((revalidation) OR Exercise[MeSH Terms]) OR Exercise) OR Life Style[MeSH Terms]) OR Life Style) OR Therapeutics[MeSH Terms]) OR Therapeutics) OR medical treatment) OR medication)))). The starting date was determined as 1 January 1990 and the search was updated till 20 April 2017. The reference lists and citations of the obtained articles were hand-searched for additional searches.

Articles were included in this review if they fulfilled the criteria described as follows (Fig. 1):

1. English-written RCTs, prospective observational studies or case–control studies, investigating both an intervention and control group, examining the relationship between arterial stiffness and (diastolic) heart failure in isolated SBP, or the effects of medication, several compounds and lifestyle (diet/exercise) on blood pressure, arterial stiffness and cardiac structure/function, in human follow-up studies (individuals acting as their own controls).
2. Individuals with isolated systolic hypertension and/or heart failure. No restrictions on age were enforced. Both sexes were included.
3. Studies investigating (primary) outcome measures (see summary measures).

Studies were excluded if populations with kidney hemodialysis/peritoneal dialysis were examined (possible hemodynamic interference), if the estimated glomerular filtration rate (eGFR) was lower than 30 ml/min per 1.73 m$^2$, if there were no ventricular or vascular changes reported or if the studies were classified as retrospective cohort and/or cross-sectional studies. In addition, review articles and case reports were not eligible for inclusion.

### Study selection and data extraction
When eligibility criteria and the search strategy were realized by three investigators (K.M.W, A.A.K. and K.D.R.), selection screening, based on title and abstract according to the *a priori* retrieved inclusion and exclusion criteria, was conducted. In case of mismatch between the investigators, inclusion of an article was based on an agreement by consensus during the selection screening. Full-text publications were reviewed by two investigators (K.M.W. and M.H.G.H.) if eligibility criteria were satisfied. Study characteristics, risk of bias within studies and results/conclusions of individual studies were reviewed independently of each other. From the selected studies, when available, the following data were extracted: study methods (design, data collection, follow-up time), participant characteristics (inclusion/exclusion, size, origin, setting), intervention/placebo treatment (type, dose, duration) and outcome measures. In case of a mismatch between first and second reviewer, agreement was achieved by consensus.

### Risk of bias
Two reviewers (K.M.W. and M.H.G.H.) independently assessed the risk of bias to ascertain the validity of the included studies. If present, discrepancies were resolved by an agreement based on consensus. Using the online Cochrane handbook for writing systematic reviews [17], sequence generation, allocation concealment, randomization, blinding of participants and personnel, proportion of drop-outs, similarity between therapies, selective outcome reporting and sponsors influence were assessed for RCTs. Prospective observational studies were assessed by the Newcastle–Ottawa Scale [18], in which selection, comparability and exposure parameters were rated.

### Summary measures
Primary outcome measures were changes in arterial stiffness, for example quantified by PWV, blood pressure, LVH, LVM and LVMI, and diastolic heart failure indices, and particularly relations between those variables. The studies included reported, on the one hand, regional pulse wave velocities (i.e. cfPWV and baPWV, based on transit time) and, on the other hand, single-point aortic stiffness (i.e. compliance and distensibility). The included studies did not utilize carotid measurements. Subsequently, from aortic stiffness estimates, we obtained estimates of aoPWV using the Bramwell–Hill equation [19]. In case compliance (CC) was reported, we used the equation $PWV = [A_0/(\rho \, CC)]^{1/2}$, whereas for distensibility (DC), we used the equation $PWV = [1/(\rho \, DC)]^{1/2}$ (see $^*$ in Table S3, http://links.lww.com/HJH/B3). Here, $A_0$ is the diastolic cross-sectional area, defined $A_0 = 0.25 \, \pi \, \text{diameter}^2$ and $\rho$ blood density, assumed 1050 kg/m$^3$. In total, six studies reported cfPWV, four studies reported baPWV and five studies reported aortic distensibility or compliance as arterial stiffness
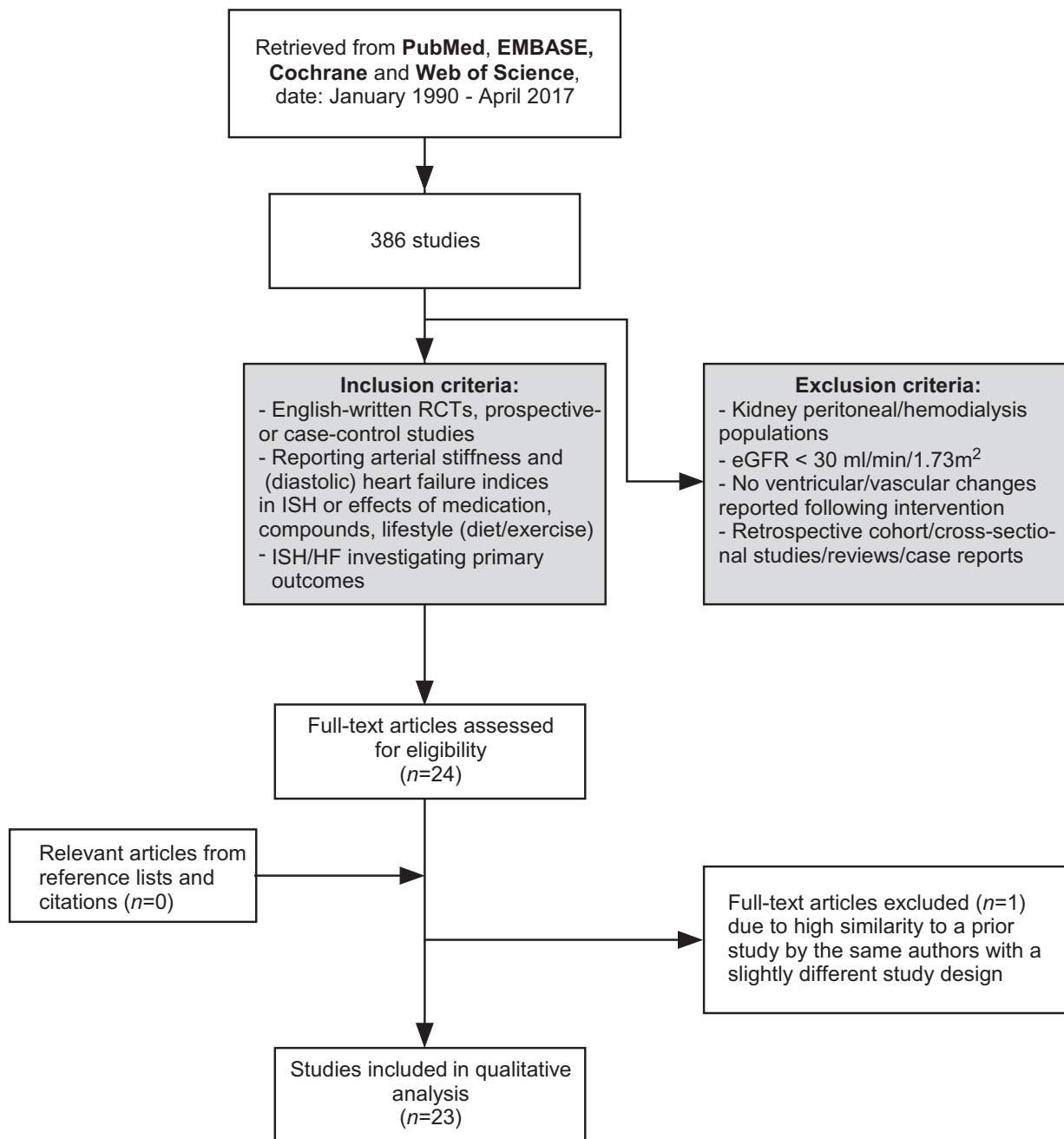
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│ Retrieved from PubMed, EMBASE,│
│ Cochrane and Web of Science, │
│ date: January 1990 - April 2017│
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      │   386 studies   │
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| Inclusion criteria: | Exclusion criteria: |
|---|---|
| - English-written RCTs, prospective-  or case-control studies<br>- Reporting arterial stiffness and  (diastolic) heart failure indices  in ISH or effects of medication,  compounds, lifestyle (diet/exercise)<br>- ISH/HF investigating primary  outcomes | - Kidney peritoneal/hemodialysis  populations<br>- eGFR < 30 ml/min/1.73m$^2$<br>- No ventricular/vascular changes  reported following intervention<br>- Retrospective cohort/cross-sectio-  nal studies/reviews/case reports |

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   ┌────────────────────────┐
   │ Full-text articles assessed│
   │     for eligibility     │
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│ Relevant articles from│ ───▶ │ Full-text articles excluded (n=1)│
│ reference lists and │        │ due to high similarity to a prior│
│ citations (n=0)    │        │ study by the same authors with a │
└───────────────────┘        │ slightly different study design  │
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   ┌────────────────────────┐
   │ Studies included in qualitative│
   │        analysis         │
   │        (n=23)           │
   └────────────────────────┘
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**FIGURE 1** Search and selection of studies.

outcome, respectively (Table 1). Although pulse pressure was included in our search strategy, we did not include these results in our analysis to avoid interpreting them as arterial stiffness measures. For studies reporting LVMI using LVM indexed by height$^{2.7}$, we recalculated LVMI using LVM/height$^2$ (see $^{\#}$ in Table S3, http://links.lww.com/HJH/B3).

## Outcome of interest and statistical analyses

For each study, we extracted average primary outcomes measures per treatment arm. The outcomes were analyzed for normality using visual inspection of histograms and quantile-quantile plots. Data were visualized using scatter plots, whereas Pearson's correlation coefficients and linear regression coefficients were calculated to explore between-study associations between changes in PWV and SBP, LVMI and SBP, and LVMI and PWV, respectively. To internally validate our findings, we performed a sensitivity analysis of the correlation and regression parameters by repeating the statistical analyses after omission of studies not specifically reporting the effect of antihypertensive medication. In addition, we repeated the statistical analyses using only the data from RCTs. A $P$ value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 24 (IBM Corp, Armonk, New York, USA).

**TABLE 1. Overview of arterial stiffness measured**

| Name | Abbreviation | Regional or single-point PWV | Studies (Ref.) |
|------|-------------|------------------------------|----------------|
| Carotid-femoral pulse wave velocity | cfPWV | regional | [20,21,27,33,39,40] |
| Brachial-ankle pulse wave velocity | baPWV | regional | [26,28,31,35] |
| Aortic pulse wave velocity | aoPWV | single-point | [22,24,36,38,41] |

baPWV, brachial pulse wave velocity; cfPWV, carotid-femoral pulse wave velocity; aoPWV, aortic pulse wave velocity.

## RESULTS

### Study selection

Using our search strategy, we identified 386 potentially relevant articles from PubMed ($n = 221$), EMBASE ($n = 1$), Cochrane ($n = 50$) and Web of Science ($n = 114$). A flow diagram of the study selection process is shown in Fig. 1. Eventually, 23 articles with a total of 2573 individuals met the inclusion and eligibility criteria and were included in this review [20–42].

### Risk of bias

The quality of the different included studies varied. For RCT-studies (Table S1, http://links.lww.com/HJH/B3), the domains 'allocation concealment', 'blinding of participants and personnel' and 'blinding of outcome assessment' constituted a plausible risk of bias for most studies. Thereby, the outcome for these individual studies is negatively influenced, which could lead to high risks of performance bias. To the contrary, most studies demonstrated adequate 'sequence generation', 'follow-up of patients' and 'similarity of therapies'. In addition, low chance of publication bias was indicated, via adequate exclusion of 'undesirable influences of sponsors' and 'selective-free outcome reporting'. For cohort studies (Table S2, http://links.lww.com/HJH/B3), the domains 'selection', 'comparability' and 'exposure' were adequate, indicating a low risk of bias. Two studies [38,42], however, constituted overall a significantly higher risk of bias, and therefore, extra attention is needed when interpreting their results.

### Study characteristics

The characteristics of included studies are summarized in Tables 2 and 3. Fourteen studies were qualified as RCTs, while the other nine were prospective observational cohort studies. The follow-up period ranged from 3 months to 4.8 years for all English-written studies. The number of participants ranged from $n = 20$ to $n = 873$. Mainly, essential hypertensive patients with or without cardiac and/or vascular alterations were included in studies in single-centre tertiary care centres in European and East Asian countries. The main exclusion criteria were cerebrovascular and/or renal disorders. The majority of the trials used antihypertensive drugs, such as angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), diuretics and beta-blockers, while other trials examined the effects of either weight loss, physical training, surgery, treatment with agalsidase beta or high doses of allopurinol. Outcome measures included changes in vascular stiffness, LVM and left ventricular diastolic function parameters, and correlations between those variables.

### Studies with vascular and ventricular outcome variables

A total of 13 studies reported values on changes in SBP, PWV and LVMI after intervention (Fig. 2). The remaining 10 studies, reporting only one or two of the outcome variables, are not displayed in Fig. 2 (data given in Table S3, http://links.lww.com/HJH/B3). At study level, changes in SBP seemingly correlated with reductions in both PWV and LVMI. Ripley *et al.* [24] reported no substantial differences between the change in SBP, PWV and LVMI among treatment arms (Fig. 2). Conversely, three studies [26,28,31] reported considerably different PWV reductions within treatment arms, despite a similar reduction in SBP. Takami and Saito [26] consisted of two treatment arms comparing two types of ARB/CCB treatment, whereas Anan *et al.* [31] consisted of three treatment arms (Fig. 2). Tomiyama *et al.* [28] consisted of an ARB treatment arm and a CCB treatment arm, respectively. Furthermore, in studies consisting of two or more treatment arms, it appeared that the study arm with the highest reduction in PWV and SBP, consistently corresponded to the treatment arm with the highest reduction in LVMI.

### Blood pressure in relation to vascular and ventricular changes

Table 4 summarizes changes in PWV and LVMI stratified by mean changes ($\Delta$) in SBP and DBP, defined by pressure ranges $\Delta$DBP at least $-7$ mmHg versus $\Delta$DBP less than $-7$ mmHg, and $\Delta$SBP at least $-13$ mmHg versus $\Delta$SBP less than $-13$ mmHg, respectively. The choice of the pressure ranges was based on twice the intrasession standard deviation for DBP and SBP, as reported earlier [14]. We found that greater reductions in blood pressure (both SBP as DBP) were indicative for greater PWV reductions, whereas for LVMI reductions, this pattern only appears to hold for greater DBP-changes (Table 4).

### Pooling of data and correlations between SBP, PWV and LVMI within studies reporting all three variables

We pooled and plotted $\Delta$SBP, $\Delta$PWV and $\Delta$LVMI data to explore potential associations among these outcome measures (Fig. 3). Regarding SBP, the proportion in reduction did not correlate significantly to the proportion in reductions of the other two outcome measures (i.e. $\Delta$PWV versus $\Delta$SBP: $r = 0.23$, $P = 0.29$; $\Delta$LVMI versus $\Delta$SBP: $r = -0.05$, $P = 0.81$). However, we found a significant positive correlation between changes in $\Delta$PWV and $\Delta$LVMI (Fig. 3,

**TABLE 2. Characteristics of included randomized control trial studies**

| | Country | Study design | Follow-up time | No. of patients | Inclusion | Exclusion | Treatment (per arm 1,2,3) | Outcome (aimed by authors) |
|---|---|---|---|---|---|---|---|---|
| Au et al. [20] | Canada | RCT | 3 months | n = 32 | Healthy active men, RET ≥ 2 years | Obesity BMI ≥30 kg/m³, history of smoking, supplements other than protein | (1) HR-RET, (2) LR-RET | BP, HR, FFM, % body fat, LVM, LVMI, cfPWV, carotid artery distensibility |
| Beaussier et al. [21] | France | RCT | 3 months | n = 164 | Essential hypertension, resistant at least three AHT drugs, including diuretic | Secondary hypertension, history of cardiovascular disease/stroke in past 3 months, AF, DMT2 uncontrolled, GFR <40ml/min | (1) Spironolactone, furosemide, amiloride, (2) Ramipril, bisoprolol | BP, cfPWV, echoCor, LVMI |
| Vizzardi et al. [22] | Italy | RCT | 6 months | n = 51 | HF, EF <40%, already treated RAAS and beta-blockers 6 months | CAD or myocardial infarction | Spironolactone | BP, aortic strain, aortic distensibility |
| Mancusi et al. [23] | Norway | RCT | 58 months | n = 873 | Hypertensive (either treated or untreated) patients aged 55–80 years with signs of LVH on ECG | Not further described | Losartan/atenolol | BP, echoCor, LVM, LVMI |
| Ripley et al. [24] | UK | RCT | 6 months | n = 34 | Essential hypertension, SBP >140mmHg, DBP >90 mmHg, LVH, ECG and CMR | Secondary hypertension, peripheral vascular disease, renal insufficiency, cardiac arrhythmias, malignancy contraindication MRI | (1) Valsartan/ moxonidine, (2) Bendroflumethiazide/amlodipine | BP, aortic distensibility, aoPWV, LVM, LVMI |
| Jekell et al. [25] | Sweden | RCT | 12 months | n = 115 | Essential hypertension with LVH and DBP (90–115 mmHg) | EF <45%, secondary hypertension, renal insufficiency, CHF, valvular heart disease | Irbesartan/atenolol | BP, echoCor, RWT, SV |
| Takami and Saito [26] | Japan | RCT | 24 months | n = 52 | Outpatients, 34–75 years | Current olmesartan, secondary hypertension, arrhythmia, CHF, history stroke or CAD, valvular heart disease, renal insufficiency, mental disorders | (1) Olmesartan/azelnidipine, (2) Olmesartan/amlodipine | BP, echoCor, LVMI, E/e', E/A, baPWV |
| Rekhraj et al. [27] | UK | RCT | 9 months | n = 33 | CAD, previous MI, AP, BP <150/90 mmHg, LVH | Allopurinol, renal insufficiency, HF, gout | Allopurinol | cfPWV, FMD, tonometry |
| Tomiyama et al. [28] | Japan | RCT | 30 months | n = 113 | SBP <180mmHg, DBP <110mmHg | Glucose >125 mg/dl, EF<50%, creatinine >2 mg/dl, AHT, ABI <0.95, DMT2 | (1) Candesartan, (2) Amlodipine | BP, echoCor, E/A, LVMI, baPWV |
| Edwards et al. [29] | UK | RCT | 10 months | n = 56 | 18–80 years, stage 2 renal failure, ACE/ARB >6 months | AP, MI, HF, DMT2, vascular disease, AF, renal failure, anaemia | Spironolactone | BP, aoPWV, cfPWV, LVM, LVMI |
| Malfatto et al. [30] | Italy | RCT | 3 months | n = 27 | Chronic systolic heart failure, stable patients | AF, mitral surgery, LV aneurysm repair, defibrillator | Physical training | Stress-test, cardiopulmonary test, echoCor, LVMI |
| Anan et al. [31] | Japan | RCT | 10 months | n = 31 | BP >140/90 mmHg | Secondary hypertension, prior AHT, organic heart disease, statins, DMT2 | (1) Valsartan, (2) Perindopril, (3) Valsartan/perindopril | BP, echoCor, baPWV, BNP, LVMI, PWT, E/A |
| deLuca et al. [32] | International | RCT | 12 months | n = 214 | BP >140/90 mmHg | Other AHT drugs | (1) Perindopril, indapamide, (2) Atenolol | BP, LVMI |
| Topouchian et al. [33] | France | RCT | 6 months | n = 69 | BP >140/90 mmHg | Stroke, renal/cardiac failure | (1) Verapamil, (2) Trandolapril, (3) Trandolapril/verapamil | BP, cfPWV, LVM, LVMI |

ACE, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AHT, antihypertensive treatment; AP, angina pectoris; ARB, angiotensin receptor blockers; baPWV, brachial pulse wave velocity; BNP, brain natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; cfPWV, carotid-femoral pulse wave velocity; CHF, congestive heart failure; CMR, cardiovascular magnetic resonance; DMT2, diabetes mellitus type 2; EF, ejection fraction; FFM, fat-free mass; GFR, glomerular filtration rate; HF, heart failure; HT, hypertension; LV, left ventricle/left ventricular; LVH, left ventricular hypertrophy; LVM, left ventricular mass; RAAS, renin-angiotensin-aldosterone-system; RET, resistance exercise training; RWT, relative wall thickness.

**TABLE 3. Characteristics of included cohort studies**

| | Country | Study design | Follow-up time | No. of patients | Inclusion | Exclusion | Treatment | Outcome (aimed by authors) |
|---|---|---|---|---|---|---|---|---|
| Kwon et al. [34] | South Korea | Cohort study | 6 months | n = 325 | Outpatient, 18–75 years, SBP <180 mmHg, DBP <110 mmHg, normal QRS | Previous/current use AHT drugs, DMT2, CHF | Follow-up after AHT | echoCor, strain, arterial stiffness, BP, ABPM, arterial distensibility |
| Watanabe et al. [35] | Japan | Cohort study | 12 months | n = 49 | BP >140/90 mmHg, CCB treatment without effect | Secondary hypertension, previous CVD, renal failure, HF | Follow-up after telmisartan | BP, echoCor, LVMI, baPWV |
| Collin et al. [36] | France | Cohort study | 54 months | n = 30 | Fabry disease, at least one cardiac/arterial measure before initiation agalsidase beta | patients treated with agalsidase, ESRD/kidney transplant, renal insufficiency, arterial measurements | Agalsidase-beta suppletion, follow-up | BP, echoCor, vascular ultrasound, cfPWV |
| Mizuguchi et al. [37] | Japan | Cohort study | 13.5 months | n = 35 | BP >140/90 mmHg | AF, CAD, HF, stroke, secondary hypertension, CHD, cardiomyopathy, DMT2 | Follow-up after telmisartan | BP, echoCor, vascular ultrasound |
| Ruvolo et al. [38] | Italy | Cohort study | 3 months | n = 20 | Male (18–60 years), high-normal BP, LVH, vascular stiffness | IHD, renal failure, DMT2, unable to perform bike test, arrhythmias, LVH | Hydrochlorothiazide, valsartan, follow-up | BP, echo LV, vascular stiffness, LVMI, SV |
| Hashimoto et al. [39] | Japan | Cohort study | 12 months | n = 61 | BP >140/90 mmHg | Secondary hypertension, CHD, HF, AF, stroke, renal insufficiency, current treatment | Follow-up after AHT | echoCor, PWB, PWA, LVMI |
| Hashimoto et al. [40] | Japan | Cohort study | 12 months | n = 43 | BP >140/90 mmHg | Secondary hypertension, renal insufficiency, major cardiovascular complications, no vasoactive drugs | Follow-up after AHT | BP, LVMI |
| Ikonomidis et al. [41] | Greece | Cohort study | 36 months | n = 56 | Morbid obese, BMI >40 kg/m² | AHT drugs, lipid decreasing, thyroid, blood glucose lowering, cardiovascular medications, auto-immune diseases | Follow-up after bariatric surgery | BP, aortic distensibility, LVM, LVMI |
| Tomiyama et al. [42] | Japan | Cohort study | 24 months | n = 90 | HT with CCB treatment | CVD or other health issues | Follow-up after AHT | BP, LVMI, cIMT |

ABPM, ambulatory blood pressure monitoring; AF, atrial fibrillation; AHT, antihypertensive treatment; baPWV, brachial pulse wave velocity; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blockers; cfPWV, carotid-femoral pulse wave velocity; CHF, congestive heart failure; DMT2, diabetes mellitus type 2; HF, heart failure; HT, hypertension; IHD, ischaemic heart disease; IMT, intima-media thickness; LV, left ventricle/left ventricular; LVH, left ventricular hypertrophy; LVM, left ventricular mass.
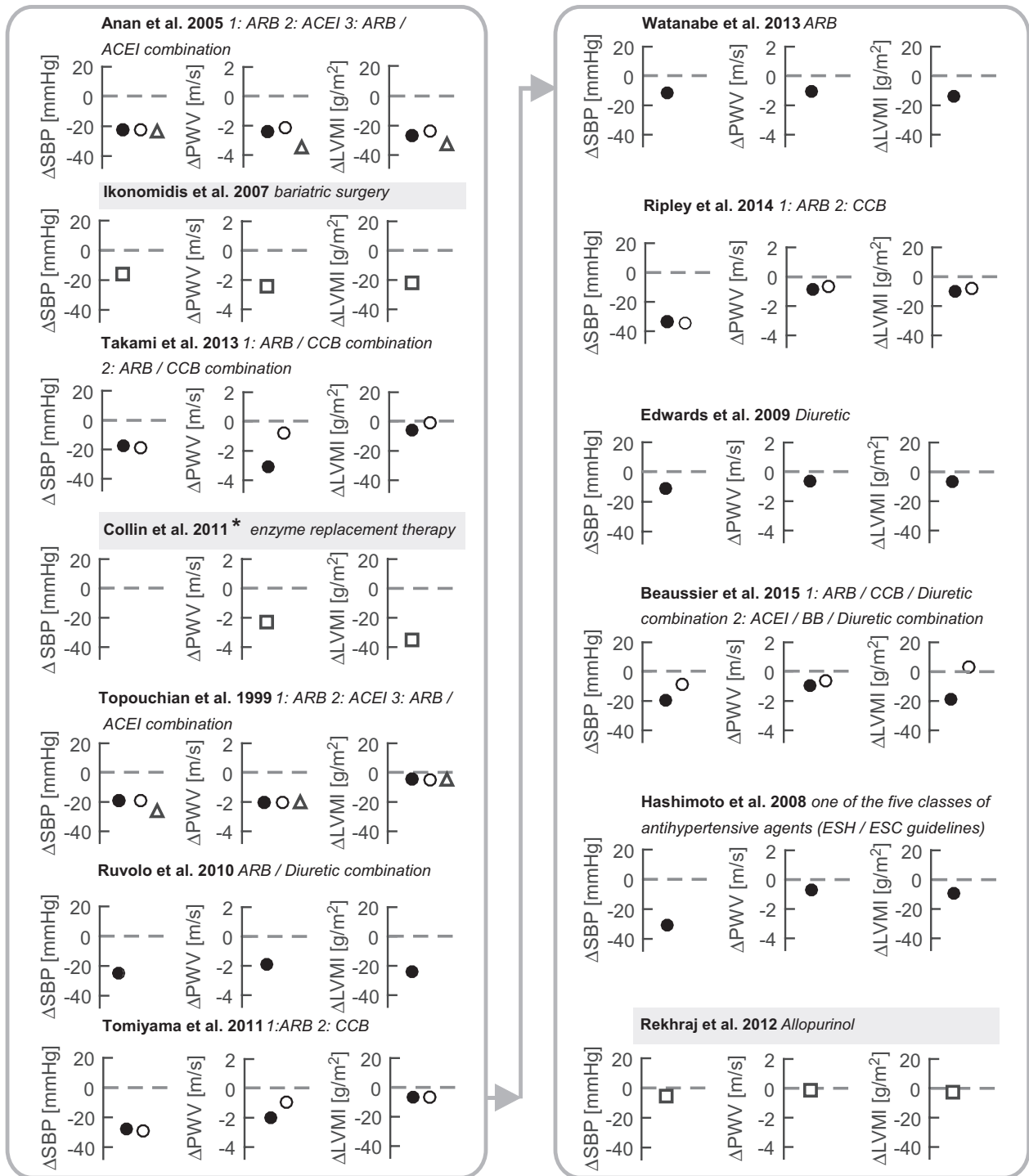
**FIGURE 2** Effect of intervention on mean changes in SBP (ΔSBP), pulse wave velocity (ΔPWV) and left ventricular mass index (ΔLVMI). Studies are listed according to magnitude of ΔPWV, from largest (top-left) to smallest (bottom-right). Ten of the 12 studies had antihypertensive medication as intervention (circles, triangles), while two (squares) had other interventions, as indicated. Symbols indicate treatment arms (i.e. closed circle = arm 1, open circle = arm 2, triangle = arm 3). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blockers; BB, beta-blockers; CCB, calcium channel blockers. *No quantitative change in SBP reported but narratively reported as '(Central) systolic blood pressure were not reduced'.

$r = 0.61$, $P = 0.003$). Furthermore, linear regression of ΔPWV on ΔLVMI suggested a 6.9 g/m² decrease in LVMI per 1 m/s decrease in PWV [95% CI = (1.9–11.8) g/m²/m/s]. The analyses were repeated following omission of the nonantihypertensive treatment studies [20,27,30,36,41]. Briefly, this caused only minor changes in the correlation and regression parameters [$r = 0.57$, $P = 0.013$, and β = 6.5 g/m²/m/s, 95%CI = (1.6–11.4) g/m²/m/s, respectively]. Similarly, we found minor changes in the correlation and regression parameters when using only data from RCTs [$r = 0.62$, $P = 0.010$, and β = 6.6 g/m²/m/s, 95% CI = (1.9–11.4) g/m²/m/s]. Given the limited amount of data points

**TABLE 4. Blood pressure changes and associated changes in pulse wave velocity and/or left ventricular mass index**

| | Changes in PWV | Changes in LVMI |
|---|---|---|
| BP change (mmHg) | ΔPWV (m/s) | ΔLVMI (g/m$^2$) |
| ΔDBP ≥ −7 | −0.9 (−3.2, −0.14) [20, 26, 27, 41] | −7.3 (−22, −2.8) [26, 27, 29, 41, 42] |
| ΔDBP < −7 | −2.0 (−3.7, −0.6) [24, 28, 31, 33, 35, 38, 39] | −11 (−35, −3.9) [23, 24, 31, 33–35, 38–40] |
| ΔSBP ≥ −13 | −0.8 (−2.4, −0.14) [20, 21, 27, 29, 35, 41] | −13 (−24, +4.5) [21, 35, 41, 42] |
| ΔSBP < −13 | −2.0 (−3.7, −0.7) [24, 26, 28, 31, 33, 38, 39] | −8.0 (−35, −2.8) [23, 24, 26, 31, 33, 34, 38–40] |

Values are presented as median (minimum, maximum).
ΔDBP and ΔSBP, change in DBP and SBP; BP, blood pressure; LVMI, left ventricular mass index; PWV, pulse wave velocity.

available for regression analysis (Fig. 3), we chose not to evaluate quadratic instead of linear associations, as this would result in overfitting. We explored possible mutual relationships between types of ΔPWV (i.e. as assessed by cfPWV, baPWV and aoPWV) with both ΔSBP and ΔLVMI (Figure S1, http://links.lww.com/HJH/B3). Our analysis did not demonstrate statistically significant associations. Nevertheless, in particular, ΔbaPWV and ΔaoPWV, but not
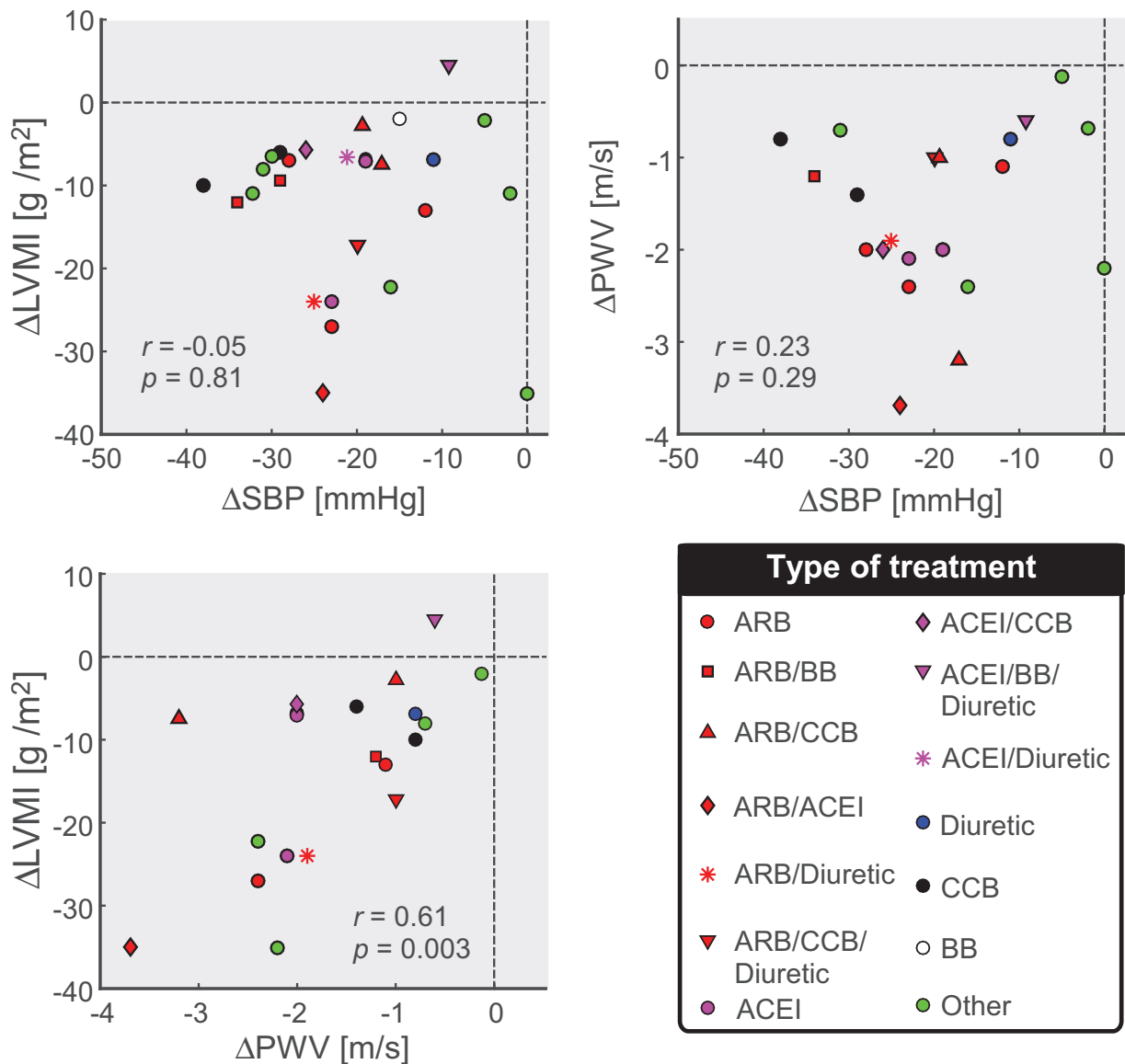


**FIGURE 3** Scatter plots of mean changes in left ventricular mass index (ΔLVMI), pulse wave velocity (ΔPWV) and systolic blood pressure (ΔSBP). Studies with two or more treatment arms were plotted as separate data points. Markers indicate treatment type, for example the prescribed antihypertensive drug class or combination of classes, respectively. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blockers; BB, beta-blockers; CCB, calcium channel blockers. *r*: Pearson correlation coefficient. *P*: statistical significance level.

$\Delta$cfPWV, showed trends with $\Delta$LVMI ($r = 0.62$, $P = 0.10$; $r = 0.83$, $P = 0.08$; $r = 0.26$, $P = 0.54$, respectively). Furthermore, $\Delta$cfPWV and $\Delta$aoPWV, but not $\Delta$baPWV, showed trends with $\Delta$SBP ($r = 0.59$, $P = 0.07$; $r = -0.85$, $P = 0.07$; $r = 0.14$, $P = 0.74$, respectively), indicating that a larger power (in future studies) might possibly lead to significant correlations. In the above analyses, a limited amount of data points was available (Figure S1, http://links.lww.com/HJH/B3).

## DISCUSSION

### Key findings
Our review of well controlled clinical intervention studies provides evidence that a decrease in arterial stiffness could contribute to the reduction of LVM in (hypertensive) patients. However, we could not obtain convincing evidence supporting the causative pathophysiological (arterial stiffening – elevated SBP – LV hypertrophy/failure)-chain. A major complication is that arterial stiffness measurements such as PWV are inherently blood pressure dependent [14,43]. In the present review, we found studies showing a significant decrease in PWV in excess of nearly 0.5 m/s, which is typically the measurement variability order of magnitude, and in excess of 1 m/s, which our group identified as the change in PWV expected for a change in DBP of 10 mmHg [14]. As such, some of the observed significant changes in PWV may partially or fully be attributable to a change in blood pressure, without a change in intrinsic arterial stiffness. We did not find a study that was appropriately designed to disentangle pressure-independent arterial stiffness effects from plain blood pressure lowering, nor are we aware of a study that extensively described SBP, PWV and LVMI changes over many time-points. We expect that changes in PWV come before changes in left ventricular mass. There were several studies included reporting arterial stiffness and ventricular structure at multiple time-points [26,28,36,41]. However, only data from Collin et al. [36] suggested that a change in PWV could precede a change in left ventricular mass. Despite the present analysis, therefore, it remains cumbersome to assess the direct effect of antihypertensive treatment on left ventricular structure and function as well as test the hypothesized causal relation between increased arterial stiffness and LVH.

### Clinical implications and future work
Our results indicate a significant positive correlation between changes in arterial stiffness and LVM. Only two of the 23 included studies [26,34] reported changes in left ventricular diastolic function indices (i.e. the outcome variables E/A and E/e', respectively). Those studies found independent statistical associations between, on the one hand, reductions in PWV and pulse wave reflection magnitude (assessed by means of augmentation index), and, on the other hand, improvements in left ventricular diastolic function (via LVMI reduction and improvements in E/A and E/e', Table S3, http://links.lww.com/HJH/B3). Takami and Saito [26] hypothesized that the mechanism involved could be a delay in arrival of the reflected pulse wave due to decreased PWV, which in turn reduces left ventricular afterload [26]. However, it should be noted that using augmentation index as a proxy for wave reflection magnitude is deemed contentious by some researchers in the field [44]. Hashimoto et al. [39] reported a positive correlation between changes in LVM and reflection magnitude, calculated using a 'gold standard' method of assessing pulse wave reflections (i.e. based on solving the physical laws of mass conservation and momentum balance [15]). The authors reported that reducing stiffness of peripheral muscular arteries, which they considered to be the root cause of increased pulse wave reflection, could be more important than reducing central arterial stiffness, in the reduction of LVM [39]. Tomiyama et al. [28] reported that candesartan leads to significantly greater reductions in stiffness of muscular arteries (i.e. assessed by brachial-ankle PWV), as compared to amlodipine [28], with similar decreases in LVMI of 7 and 6 g/m$^2$, respectively.

In summary, our results suggest that therapeutic agents that aim to lower arterial stiffness may lead to greater reductions in LVM. However, further clinical trials with multiple follow-up measurements, using pressure-independent arterial stiffness indices, are required to establish the causative role of arterial stiffness-lowering in reduction of LVM. To achieve the latter, a stiffness index such as $CAVI_0$ could be a promising candidate [43]. In addition, directing more attention to pulse wave reflection indices may further advance insight into LVM reduction [26,39]. Of particular interest are (lifestyle or surgical) interventions improving physical activity and diet, as these kinds of trials provided promising results in terms of arterial stiffness and left ventricular diastolic function improvements [20,27,30,36,41], without invoking per se the effects of direct actions of antihypertensive drugs on the cardiovascular system.

### Limitations
Our review is limited by its reliance on published data causing an inherent risk of publication bias, as neutral studies (without changes in LVMI or PWV) are less likely to be accepted by publishers. A general conclusion about the effect size of lowering blood pressure and arterial stiffness on LVH is difficult, as the quality of the studies was variable (i.e. quality rating ranging between 2 and 8 points out of 10 for RCTs, and between 5 and 9 points for cohort studies, Table S1 and S2, http://links.lww.com/HJH/B3). Most studies quantified arterial stiffness using carotid-femoral PWV or brachial-ankle PWV, calculated using pulse transit time and path length. For studies reporting either a change in compliance or distensibility, we were limited to calculating an estimate of PWV using the Bramwell–Hill equation. Regional (i.e. carotid-femoral and brachial-ankle) PWV values are physically different compared with single-point (i.e. aortic) PWV values, calculated using the Bramwell–Hill equation. However, previous work including patient studies [45,46] and mechanistic computational studies [47] showed reasonable proportionality between regional PWV and single-point PWV. Also, the study of Chow and Rabkin [48] showed appropriate proportionality between baPWV and cfPWV. Therefore, we believe that pooling of changes in cfPWV, baPWV and aoPWV can be justified. We, however, cannot exclude that pooling the various methodologies of PWV assessment influenced the associations we found. Furthermore, considering the

heterogeneity in antihypertensive treatment and the limited number of studies included, we have not been able to conduct antihypertensive drug class specific analyses. Lack of correlation between changes in SBP and LVMI could be related to the fact that most studies included in this review performed office BP measurements instead of 24-h ambulatory BP measurements. Office blood pressure measurements contain more variable SBP readings, for example due to interindividual differences in white-coat effect. Previously, it was reported that in hypertensive children, 24-h SBP relates with LVMI, but not with office SBP [49]. Lastly, minor limitations of this review include our language restriction for only English written articles, and our inclusion of non-RCT studies, which in the hierarchy of evidence are inferior to RCT studies.

## Conclusion

This review demonstrates that there is evidence in well controlled clinical intervention studies that a decrease in arterial stiffness is associated with a reduction of left ventricular mass. To eliminate blood pressure dependent effects for the correlation between arterial stiffness and left ventricular structure, blood pressure independent markers should be used in future studies. In that way, better identification of potential targets for antihypertensive drug treatment may be facilitated. In addition, the potential of lifestyle interventions (e.g. physical activity and diet) in the research field remains to be emphasized.

## ACKNOWLEDGEMENTS

### Conflicts of interest
The authors have no conflicts of interest.

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