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Echocardiographic aortic root dilatation in hypertensive patients: a systematic review and meta-analysis

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Abbreviations: ABPM, ambulatory blood pressure monitoring; ARD, aortic root dilatation; BP, blood pressure; BSA, body surface area; CI, confidence interval; HBP, high blood pressure; LVH, left-ventricular hypertrophy; LVM, left-ventricular mass; OR, odds ratio; SoV, sinuses of Valsalva

Abstract

Objective: The risk of thoracic aortic dissection is strictly related to the diameter of the ascending aorta. Arterial hypertension represents a major risk factor for the development of aortic dissection and is thought to be directly involved in the pathogenesis of aortic aneurysms. Recent studies have suggested a high prevalence of aortic root enlargement in the hypertensive population, but evidence of a direct link between blood pressure values and size of the aortic root has been inconclusive so far. The aim of the current study was to evaluate prevalence of aortic root dilatation (ARD) in the hypertensive population and to assess the correlates of this condition.

Methods: Medical literature was reviewed to identify articles assessing prevalence of echocardiographic ARD in hypertensive patients.

Results: A total of eight studies including 10 791 hypertensive patients were considered. Prevalence of ARD in the pooled population was 9.1% with a marked difference between men and women (12.7 vs. 4.5%; odds ratio 3.15; 95% confidence interval 2.68–3.71). Hypertensive patients with ARD and those with normal aortic root size had similar office blood pressure values, but the former were older and had a significantly higher left-ventricular mass (0.52 SDs, 95% confidence interval 0.41–0.63).

Conclusion: ARD is a common phenotype in hypertensive patients, with men showing a markedly higher susceptibility, but office blood pressure values do not appear to be directly associated with aortic root diameter.

INTRODUCTION

Incidence of life-threatening vascular complications such as thoracic aortic dissection and rupture appears strictly related to the diameter of the ascending aorta [1]. Arterial hypertension represents a major risk factor for aortic dissection [2]. Data from the International Registry of Acute Aortic Dissection state that 71% of 519 patients with aortic dissection were hypertensive [3]. Furthermore, aortic root size has been shown to predict cardiovascular mortality independently of other cardiovascular risk factors in a large cohort of elderly patients [4].

Hypertension causes increased stress on the aortic wall and for this reason is commonly regarded as a predisposing condition for the development of thoracic aorta aneurysms [2]. However, the link between hypertension and aortic root dimensions remains controversial [5]. In a cross-sectional evaluation of patients enrolled in the HyperGEN study [6], prevalence of aortic root dilatation (ARD) was similar between 2096 hypertensive patients and 361 normotensive individuals, and body surface area (BSA)-adjusted diameter measured at the sinuses of Valsalva (SoV) was marginally larger in the normotensive individuals. Both post-mortem evaluations [7,8] and imaging studies [9–17] have tried to clarify this relation with inconsistent and sometimes conflicting results. Nonetheless, recent data suggest a high prevalence of echocardiographic ARD in the hypertensive population, with significant disparity between male and female patients [6,18–20].

The present systematic analysis aims to assess prevalence of ARD among hypertensive patients with a specific focus on sex-related differences. Blood pressure (BP) values and clinical features of patients with and without ARD were then compared.

METHODS

Search strategy and study selection

Medical literature was reviewed to identify articles evaluating prevalence of ARD in hypertensive patients, as assessed by transthoracic echocardiography. In order to be considered eligible, the following data had to be reported: prevalence of echocardiographic ARD; definition of ARD; details concerning the measuring technique and the anatomical level at which the aortic root was assessed; inclusion of patients affected by hypertension defined according to the current guidelines; publication in peer-reviewed journals. Studies involving patients with Marfan syndrome or selected subpopulations of hypertensive patients with specific comorbidities were excluded (bicuspid aortic valve, valvulopathies, secondary forms of hypertension). Case–control studies (i.e. studies comparing selected hypertensive patients with ARD and hypertensive patients with normal aortic root) were also excluded.

We conducted a computerized search using PubMed, OVID and ISI-Web of Knowledge databases from their inception through 7 October 2013.

Keywords such as 'dilatation or enlargement or ectasia' and 'aortic root or Valsalva' and 'hypertension' were used in various combinations; references of selected papers and pertinent reviews were used to complement the initial search. Investigators first screened titles and abstracts and then reviewed the full text.

Relevant data were extracted by two independent investigators (M.C. and S.T.), and controversies were concluded by a third investigator (F.R.). For three studies [6,21,22], the authors were contacted to request supplementary data regarding prevalence of ARD in male and female patients separately; the requested information was provided in two cases [6,21].

When the same research group had published more than one paper, we investigated possible overlapping of the study sample and, when needed, only the most recent work was considered. In particular, for one study, the author provided the original database so that it was possible to exclude a subgroup of patients already featured in a multicentric study to which the same author had contributed. Furthermore, prevalence of ARD was recalculated by using a definition more similar to the definition used in other papers [18].

Figure 1 details the research process. Of the 10 publications identified according to our inclusion and exclusion criteria, eight were considered for the final analysis [6,18–24] after exclusion of two studies due to overlapping of the sample with other works already included. Table 1 summarizes the main characteristics of the included studies.

Statistical analysis

The first part of the analysis aimed to assess the average prevalence of ARD among hypertensive patients; the analysis was repeated separately for female and male hypertensive patients when data were available. Average prevalence of ARD in the pooled population was computed by performing a study-level meta-analysis, considering prevalence of ARD as a raw proportion. Prevalence between men and women was compared by calculating the odds ratio (OR) for ARD between the two sexes. Average prevalence of ARD is expressed as percentage [95% confidence interval (CI)].

In the second part of the analysis, hypertensive patients with ARD were compared to those with normal aortic root size. BP values and age were compared by calculating the mean difference between the two groups for each study. Left-ventricular mass (LVM) was computed as standardized mean difference because LVM indexed for height2.7, LVM indexed for BSA or unadjusted LVM was used, depending on which information was available in the original paper. A subgroup analysis was performed to rule out heterogeneity between studies performed by our group and works from other groups.

The proportion of variability explained by true heterogeneity (i.e. between-studies variability) was estimated by calculating the I2 for each analysis. Random-effect models were used due to high heterogeneity of the study samples. Assessment for publication bias was performed by inspection of funnel plots followed by the trim-and-fill procedure. The restricted maximum likelihood (REML) method was used for all computations. R software version 3.0.1 [25] with the Metafor package version 1.9–2 [26] was used for statistical analysis.

RESULTS

Characteristics of the studies

From eight studies, 10791 hypertensive patients (5280 women and 5511 men) were included in the final analysis (Table 1). Although specific data regarding ethnicity was generally not available, four studies included mostly Caucasian patients [18–21], three had a mixed cohort consisting mostly of Caucasians and African-Americans [6,23,24], and one study included only Asian hypertensive patients [22]. Overall, more than 80% of the pooled population was Caucasian and the results of the analysis should not be generalized to other settings. The cardiovascular profile of the enrolled patients varied, ranging from younger patients with never-treated hypertension [21] to older patients with left-ventricular hypertrophy (LVH) and severe uncontrolled hypertension [23]. All studies defined hypertension in the presence of BP values above 140/90 mmHg or of concomitant antihypertensive therapy.

Echocardiographic criteria for aortic root dilatation

All eight studies assessed presence of ARD with transthoracic echocardiography; measures were obtained at end diastole at the SoV level in all studies; in one study additional anatomical sites of the ascending aorta were considered [22]. The aortic diameter was measured by M-mode tracings under two-dimensional control. Definition of ARD differed between the studies: in two studies [6,23], BSA-indexed aortic diameter was compared to cut-off values from a reference population without further adjustment for sex; in five studies [19–21,24,27], the definition was based on sex-specific cut-offs of unadjusted aortic root diameter; only one study [22] used a single cut-off without accounting for body size or sex; due to lack of sex-specific data on prevalence, this study was not included in the analysis by sex.

Prevalence of aortic root dilatation in the pooled population

Average prevalence of ARD in the pooled population was 9.1% (95% CI 6.1–12.1) and ranged from 3.7 to 16.7% across the individual studies. The presence of a consistent amount of true heterogeneity among the studies was confirmed by the large value of I2 (96.99%). A meta-regression was performed for variables with known or presumed influence on aortic root size (age, DBP, SBP, mean BP and pulse BP values), but did not yield significant results. However, the statistical power of such an analysis is low in the presence of a high degree of heterogeneity and with a relatively small number of studies. A sensitivity analysis was performed, showing that the effect size was not significantly affected by single-study effect. No publication bias was found for prevalence of ARD in the pooled population.

Prevalence of aortic root dilatation according to sex

For seven out of the eight studies, sex-specific ARD prevalence was either reported or detailed data could be obtained from the authors. Prevalence of ARD was 12.7% (95% CI 8.3–17) among male (N = 5321) and 4.5% (95% CI 2.7–6.2) among female patients (N = 5122). Prevalence of ARD was then directly compared between men and women in each study, confirming a significantly higher frequency among men (OR 3.15; 95% CI 2.68–3.71; Fig. 2); this finding was highly consistent among all studies (I2 = 0%). No publication bias was evident for male patients, whereas a possible small-study effect could be observed for female patients; correction with the trim-and-fill method lead to a minor change in the observed effect size (adjusted OR 3.24; 95% CI 2.77–3.79).

Comparison of hemodynamic and clinical features of patients with and without aortic root dilatation
For six out of the eight studies, hemodynamic, clinical and echocardiographic characteristics were reported separately for patients with and without ARD. The analysis was performed separately for male and female patients if these data were available for each sex. No difference was found between SBP and DBP values of individuals with and without ARD (Fig. 3). No difference emerged even when BP was expressed in terms of mean arterial pressure (MAP) and pulse pressure. As illustrated in Fig. 4, patients with aortic root enlargement were significantly older (mean difference 4.3 years, 95% CI 2.7–5.9) and had a higher LVM (standardized mean difference 0.52 SDs, 95% CI 0.41–0.63).

DISCUSSION

Echocardiographic ARD was found in nearly 10% of hypertensive patients in the pooled population with a marked difference between male and female patients. Prevalence in the pooled population varied among the studies, reflecting the heterogeneity of the clinical characteristics of patients enrolled. The different definitions of ARD adopted can be grouped into two categories: sex-specific cut-offs for unadjusted aortic root diameter and cut-offs based on BSA-indexed aortic diameter without further adjustment for sex. Recent data support the existence of sex-related differences in aortic root diameter even after adjustment for body size [16,29], and the use of sex-specific equations to predict normal values of aortic root size should be preferred.
Nonetheless, a marked difference in prevalence of ARD between men and women could be observed in all studies, independently of the definition. A greater propensity to outward aortic remodeling for men has been highlighted in a longitudinal analysis of more than 3000 Framingham patients [15], and this finding is consistent with the high male-to-female ratio seen in patients with thoracic aortic dissection [3]. Sex steroids have been shown in vitro to regulate collagen and elastin deposition and gene expression of matrix metalloproteinases [30]; hormonal factors may therefore partially explain the striking predisposition to aortic enlargement observed for men.
Considering the significant prevalence of ARD in patients with high BP (HBP), it would seem intuitive to consider ARD as a manifestation of hypertensive target organ damage. However, BP values did not differ between patients with and without ARD in our pooled population. Even when considering studies with a different design, the evidence supporting such an assumption is limited as results from past works have often been conflicting [9,14,15,17,31,34]. A small direct relation between DBP and aortic root diameter was found in a sample of 4001 patients from the Framingham Heart Study [31]; in the same study, SBP was inversely related to aortic root size. These findings were confirmed in a longitudinal analysis of the Framingham population, where an increase of aortic root size was directly related to MAP values, whereas the relation was inverse for pulse pressure [15]. The opposite effects observed for MAP and pulse pressure on aortic root size have forced a reconsideration of the classic theory according to which passive aortic dilatation and stiffening occur due to fragmentation of elastin in response to aging and increased pressure load. In line with this traditional view, aortic root enlargement and increase in pulse pressure are two

closely related phenomena, both linked to vascular aging [32]. The alternative thesis supports a reverse causal relationship between BP and aortic size: a small aortic root would be linked to a higher pulsatile pressure due to a mismatch between aortic flow and diameter, resulting in elevation of the forward pressure wave amplitude [33]. Yet, a longitudinal study of 3195 Framingham study participants with normal BP values at baseline failed to show an association between incidence of hypertension and aortic root size [14]. The hypothesis that the link between aortic root size and BP may be modulated by the specific pattern of hypertension was not confirmed in a cross-sectional evaluation of 1256 Taiwanese patients after adjustment of aortic dimensions for age [34], highlighting the importance of correctly matching cases and controls for those parameters which are known to be the main determinants of aortic size, namely sex, age and body size. Kim et al.[17] evaluated the size of ascending aorta in 110 normotensive individuals and 110 hypertensive patients matched for age and sex: after indexing aortic size for BSA, no significant difference was found between the two groups at the aortic annulus or at the SoV.

Several factors could contribute to the inconsistency among the aforementioned studies. Firstly, cross-sectional studies often fail to match hypertensive patients and normotensive individuals for age, sex and body size. Furthermore, whereas most works have relied on clinical BP measurements, central hemodynamics and ambulatory BP values might be stronger predictors [21]. Additionally, assuming a relation between BP and aortic root diameter exists, duration of hypertension must be taken into account, as suggested by the relatively low prevalence of ARD (3.7%) among young, never-treated hypertensive patients with no evidence of cardiovascular comorbidities [21]. Lastly, antihypertensive therapy may conceal the relation between BP values and aortic size [6].

Additional aspects of this analysis should be discussed. LVM was significantly greater in patients with aortic root enlargement than in those with normal aortic root. Regression analyses confirm that LVM is a strong predictor of ARD among hypertensive patients [19,21,24]. Although this relationship could be simply mediated by hypertension itself, our finding that BP levels – unlike LVM – are similar between patients with and without ARD does not support this view. Cuspidi et al.[35] observed a high prevalence of right-ventricular hypertrophy in patients with systemic hypertension and hypothesized that both mechanical and hormonal factors (specifically, increased sympathetic tone and activation of the rennin–angiotensin–aldosterone axis) might mediate the indirect response of the right heart to systemic arterial pressure. Similarly, Schmieder [36] suggested that nonhemodynamic mediators could explain part of the great variance of LVM observed in hypertensive patients with similar degrees of hypertension. Supporting this view, a recent trial showed that the reduction in the rate of aortic root enlargement induced by losartan in adults with Marfan syndrome is not related to the BP-lowering effect [37]. Given the dubious correlation between BP values and aortic root size, the role of hormonal mediators in aortic root enlargement warrants further research.

Some potential limitations of this analysis should be addressed. Lack of normotensive controls within each study may have biased our interpretation of the 'high' prevalence of ARD in hypertensive patients. However, it should be pointed out that in seven out of the eight studies, dilatation was defined for aortic root diameter above the 97th percentile of a reference normotensive population. Therefore, our average prevalence of 9.1% is beyond what could be expected if normotensive individuals and hypertensive patients fit under the same normal distribution of aortic root size. Unfortunately, absence of age-specific reference values might have led to overestimation of ARD prevalence had the study sample been significantly older than the reference population; use of recently proposed equations [29] will avert such shortcomings in future works.

A second possible limitation concerns the analysis of features associated with ARD, specifically BP values. Although no hemodynamic parameter was significantly associated with ARD and it is unlikely that any meaningful difference in office BP values could have been overlooked, ambulatory BP values represent a more reproducible index of BP load and the use of ambulatory BP monitoring (ABPM) in this field of research should be strongly encouraged.

The possibility that antihypertensive treatment may affect the relationship between BP values and aortic root size has been acknowledged by some authors [6]. Unfortunately, most studies enrolled a significant percentage of treated patients. In the only study focusing specifically on never-treated patients, office BP was not independently related to aortic root size, whereas average night-time DBP was the only hemodynamic parameter associated with ARD in multivariate analysis. Both baseline echocardiographic assessment of never-treated hypertensive patients and longitudinal echocardiographic tracking of patients receiving a specific class of antihypertensives represent valuable yet scarce sources of data for a better understanding of the pathogenesis of ARD.

Another limitation concerns the high heterogeneity of the study samples and the diversity of definitions of ARD. However, heterogeneity did not appear to influence the two main findings of our work: the marked sex-related difference in prevalence of ARD and the lack of correlation between presence of ARD and office BP values.

In conclusion, the pathogenesis of aortic root enlargement is still unclear. Despite being traditionally considered a form of hypertensive target organ damage, BP values were not directly associated with aortic root enlargement in our pooled population of more than 10 000 patients, and conflicting results from other works not included in our analysis fail to bring clarification. However, prevalence of ARD was high (12.7%) among hypertensive men, suggesting ARD is a common phenotype in these patients. Since remodeling of the aortic root in hypertensive patients does not appear to be driven by BP values, the role of other mechanisms such as hormonal factors should be investigated. The adoption of a uniform definition of aortic root enlargement and the use of recently validated equations [29] will facilitate further research in this field and will help clarify the correlates of this condition.

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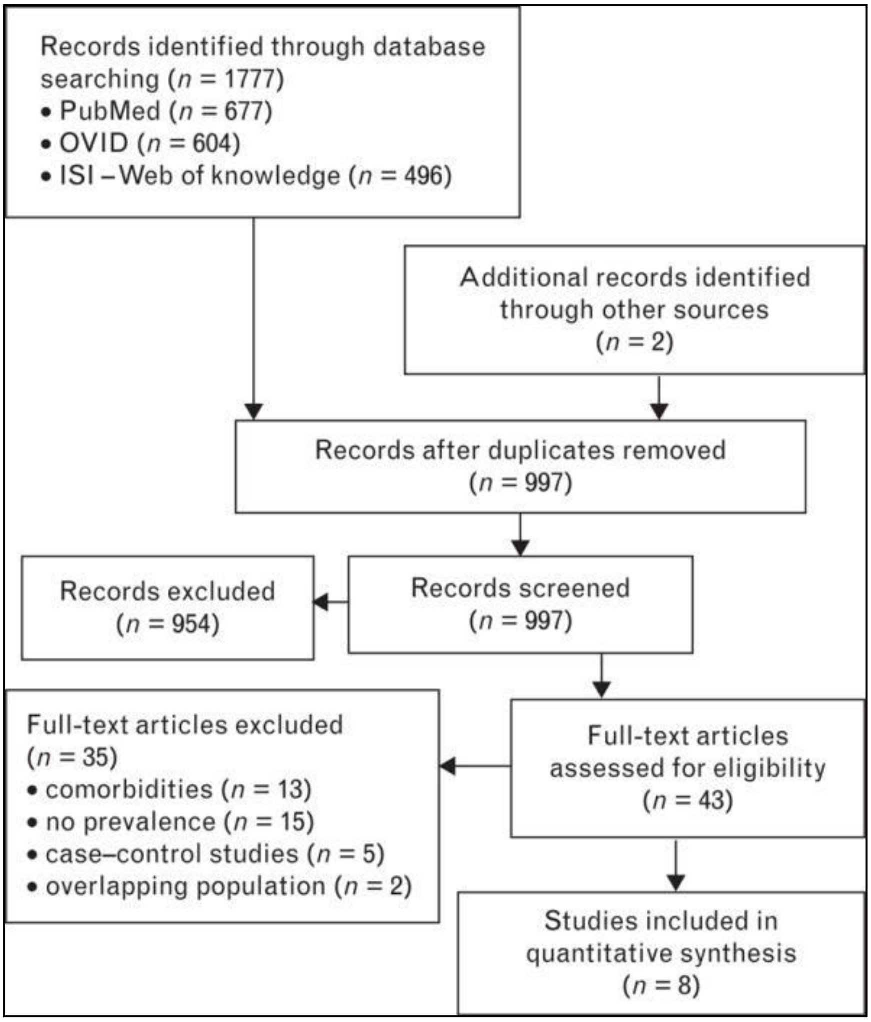

FIGURE 1: Flow chart for the selection of the included papers.

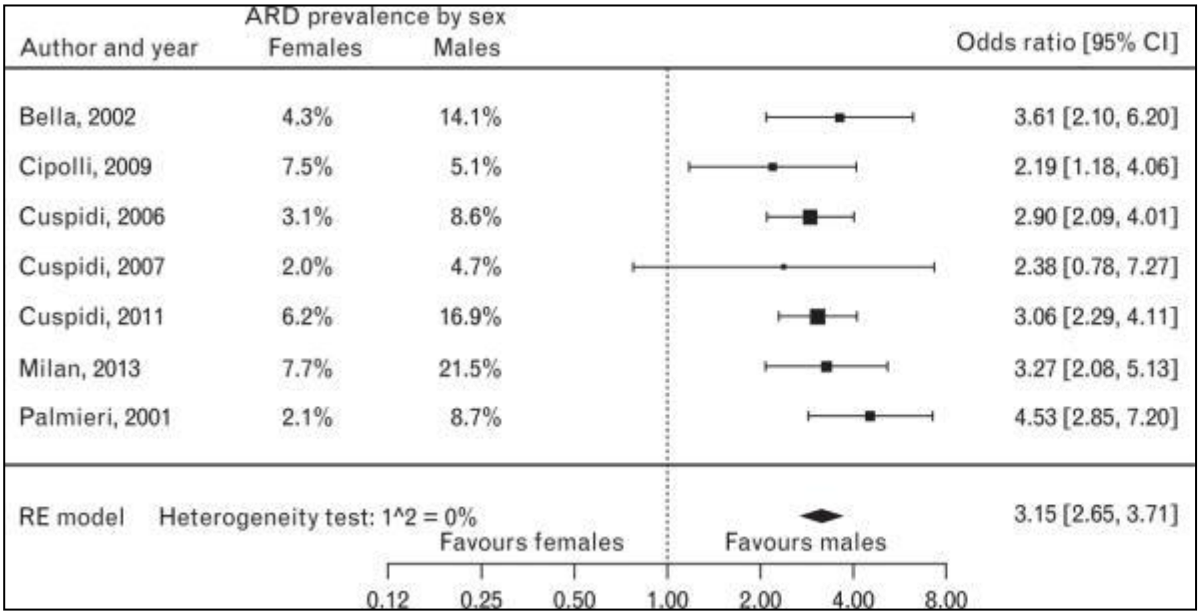

FIGURE 2 . Comparison of prevalence of aortic root dilatation in men (N = 5122) and women (N = 5321).

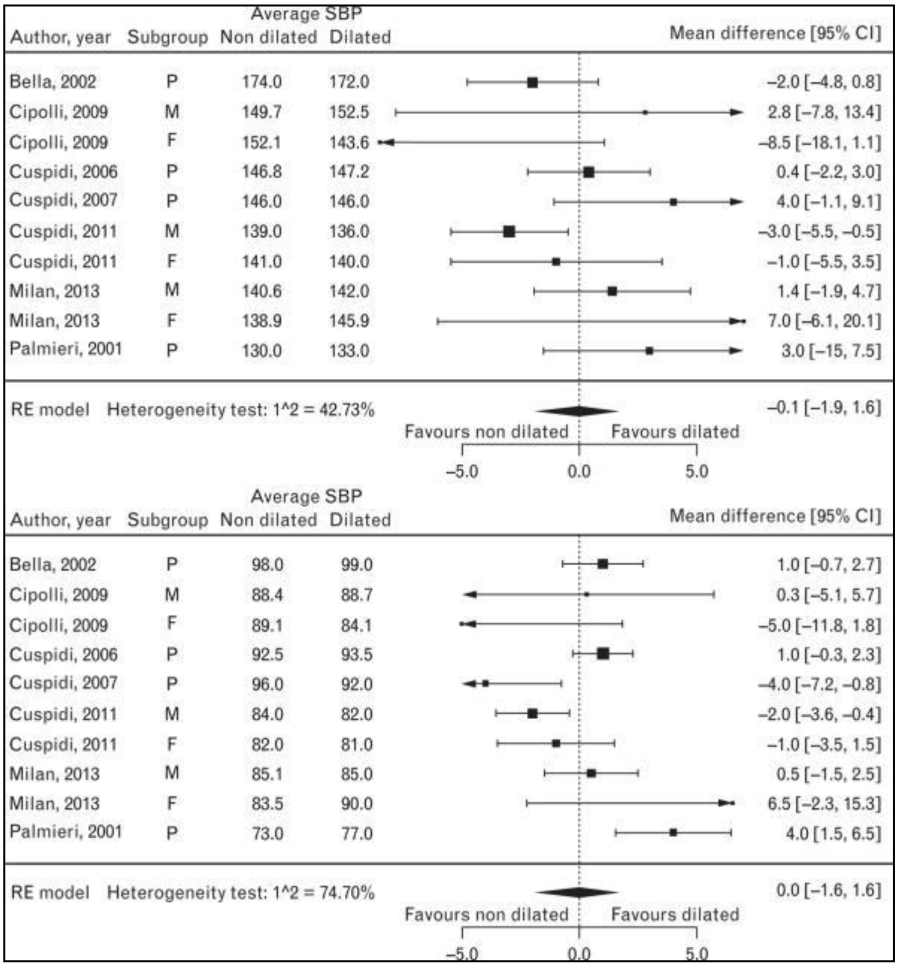

FIGURE 3 . Comparison of SBP and DBP values between hypertensive patients with and without aortic root dilatation. Subgroup: M = men only; F = women only; P = pooled

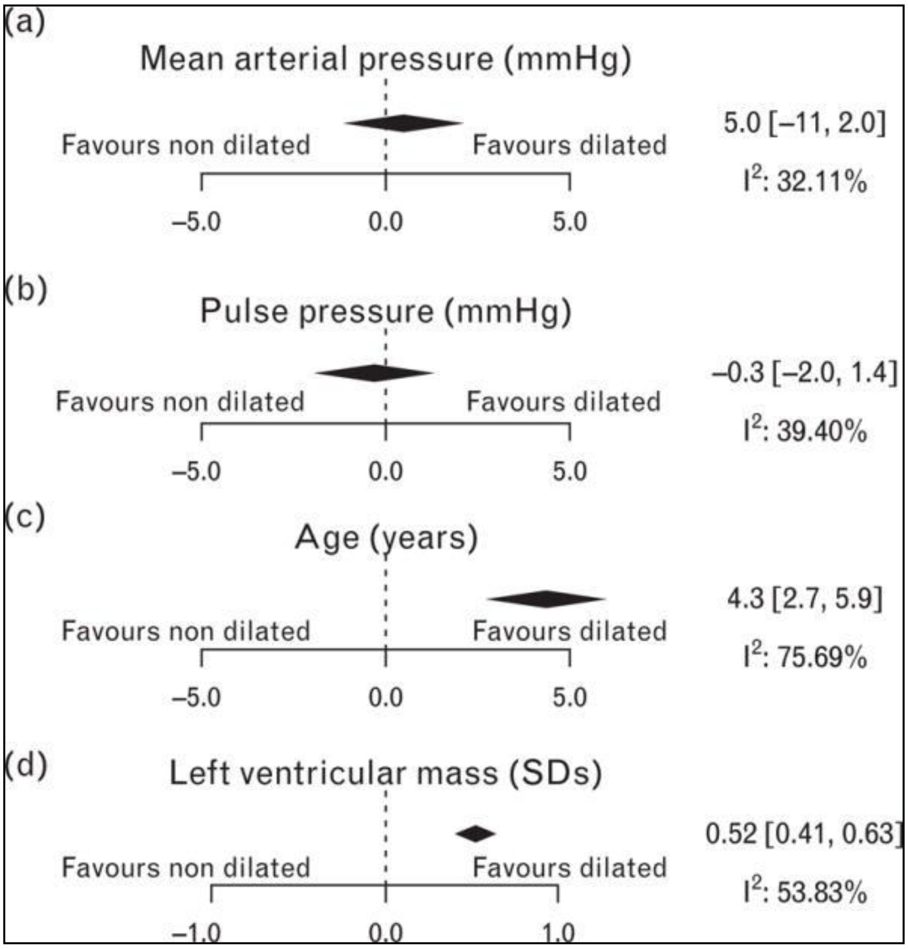

FIGURE 4 . Comparison of hemodynamic, clinical and echocardiographic features between hypertensive patients with and without aortic root dilatation. (a) Difference in mean arterial pressure, expressed in mmHg. (b) Difference in pulse pressure, expressed in mmHg. (c) Difference in age, expressed in years. (d) Difference in left-ventricular mass, expressed in SDs.

Author, year	Sample size	Age	Men (%)	BMI (kg/m^2)	Average number of antihypertensives or % of treated patients	Patient characteristics	Definition of ARD	ARD (%)
Bella *et al.* [23], 2002	947	66 ± 7	59%	25.9	ARD: 100% treated; not ARD: 100% treated	Subpopulation of the LIFE study (hypertension with BP 160–200/95–115 and LVH by EKG criteria)	Diameter at the SoV >2 SDs above the regression line with BSA in a reference population [28]	10.0
Cipolli *et al.* [24], 2009	438	57 ± 13	39%	31.3	ARD: 2.6; not ARD: 2.6	Consecutive outpatients with hypertension and echocardiographic LVH	Diameter at the SoV ≥37 mm in women, ≥40 mm in men; (>2 SD of a previously evaluated outpatient population)	10.5
Cuspidi *et al.* [20], 2006	3366	53 ± 13	52%	26.3	ARD: 2.2; not ARD: 1.9	Essential hypertensive patients enrolled in the ETODH registry [27]	Diameter at the SoV >37 mm in women, >39 mm in men; (97th percentile of a previously evaluated outpatient population)	6.1
Cuspidi *et al.* [21], 2007	519	46 ± 12	62%	25.4	ARD: 0, not ARD: 0	Consecutive never-treated patients with stage I–II hypertension	Diameter at the SoV >37 mm in women, >40 mm in men (98th percentile of a previously evaluated healthy outpatient population)	3.7
Cuspidi *et al.*, [19], 2011	2229	62 ± 13	52%	27.5	ARD: 2.5; not ARD: 2.3	Consecutive treated and untreated hypertensive patients referred for TTE by general practitioner	Diameter at the SoV >37 mm in women, >39 mm in men [20]	11.8
Milan *et al.* [18], 2013	939	52 ± 12	65%	26.5	ARD: 1.9; not ARD: 1.5	Essential hypertensive patients referred for organ damage evaluation	Diameter at the SoV >37 mm in women, >39 mm in men (prevalence recalculated from original dataset)	16.7
Palmieri *et al.* [6], 2001	2005	55 ± 11	37%	31.9	ARD: 82% treated; not ARD: 88% treated	Cohort of the HyperGEN study (HBP by age 60 and at least 1 sibling with HBP)	Diameter at the SoV >97.5th percentile of values predicted by patient's BSA in a reference population [28]	4.5
Tang *et al.* [22], 2010	348	68 ± 10	55%	23.6	NA	Consecutive essential hypertensive patients admitted for cardiovascular risk factor control	Diameter ≥38 mm at ≥1 of the following: aortic annulus; SoV; sinotubular junction; maximal diameter of proximal ascending aorta	10.4

ARD, aortic root dilatation; BSA, body surface area; EKG, electrocardiography; ETODH, Evaluation of Target Organ Damage in Hypertension study; HBP, high blood pressure; LVH, left-ventricular hypertrophy; SoV, sinuses of Valsalva; TTE, transthoracic echocardiography

TABLE 1 Main characteristics of the studies included in the analysis