OPEN

Independent Influence of Overweight and Obesity on the Regression of Left Ventricular Hypertrophy in Hypertensive Patients

A Meta-analysis

Kun Zhang, MD, Feifei Huang, MD, Jie Chen, MPH, Qingqing Cai, MD, PhD, Tong Wang, MD, PhD, Rong Zou, MD, Zhiyi Zuo, MD, PhD, Jingfeng Wang, MD, and Hui Huang, MD, PhD

Abstract: Overweight and obesity are associated with adverse cardiovascular outcomes. However, the role of overweight and obesity in left ventricular hypertrophy (LVH) of hypertensive patients is controversial. The aim of the current meta-analysis was to evaluate the influence of overweight and obesity on LVH regression in the hypertensive population.

Twenty-eight randomized controlled trials comprising 2403 hypertensive patients (mean age range: 43.8–66.7 years) were identified. Three groups were divided according to body mass index: normal weight, overweight, and obesity groups.

Compared with the normal-weight group, LVH regression in the overweight and obesity groups was more obvious with less reduction of systolic blood pressure after antihypertensive therapies ($P < 0.001$). The renin–angiotensin system inhibitor was the most effective in regressing LVH in overweight and obese hypertensive patients (19.27 g/m^2, 95% confidence interval [15.25, 23.29], $P < 0.001$), followed by β-blockers, calcium channel blockers, and diuretics. In the stratified analysis based on blood pressure measurement methods and age, more significant LVH regression was found in 24-h ambulatory blood pressure monitoring (ABPM) group and in relatively young patients (40–60 years' old) group ($P < 0.01$).

Overweight and obesity are independent risk factors for LVH in hypertensive patients. Intervention at an early age and monitoring by ABPM may facilitate therapy-induced LVH regression in overweight and obese hypertensive patients.

(*Medicine* 93(25):e130)

Abbreviations: ABPM = ambulatory blood pressure monitoring, ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers, β-blockers = beta-receptor blockers, BMI = body mass index, BP = blood pressure, CCB = calcium channel blockers, CI = confidence interval, DBP = diastolic blood pressure, LVM = left ventricular mass, LVH = left ventricular hypertrophy, LVMI = left ventricular mass index, RAS = renin–angiotensin system, RASI = renin–angiotensin system inhibitor, RCT = randomized control trial, SBP = systolic blood pressure, WHO = World Health Organization, WMD = weighted mean difference.

INTRODUCTION

Overweight and obesity are a major health problem worldwide and lead to a large number of deaths annually.[1] Overweight and obesity are associated with left ventricular hypertrophy (LVH), which is a strong predictor of cardiovascular morbidity and mortality.[2] It is known that overweight and obesity not only are definitive risk factors for hypertension, but also play a key role in the process of LVH.[3] Previous studies have shown that body mass index (BMI), the most commonly used index of adiposity, independently predicts left ventricular mass (LVM).[4] Undergoing substantial weight loss through bariatric surgery and diet restriction reduced LVH in overweight and obese subjects independent of changes in blood pressure (BP).[5,6] However, there are different viewpoints. Hsuan et al[7] considered that BP reduction was the major determinant for the regression of LVH in the early stage of surgical weight reduction. In ob/ob mice, although caloric restriction induced weight loss, no decrease in wall thickness and a lesser change in myocyte size were found.[8] Thus, the role

Editor: Marco Alves.
Received: June 15, 2014; revised: July 24, 2014; accepted: August 24, 2014.
From the Department of Cardiology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University (KZ, FH, JW, HH); Guangdong Province Key Laboratory of Arrhythmia and Electrophysiology (KZ, FH, JC, TW, RZ, JW, HH); Department of Radiation Oncology, Sun Yat-sen Memorial Hospital (JC); Department of Internal Medicine, Cancer Center, Sun Yat-sen University, Guangzhou, China (QC); and Department of Anesthesiology, University of Virginia Health System, Charlottesville, VA, USA (ZZ).
Correspondence: Dr Hui Huang, Department of Cardiology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, 107 West Yanjiang Road, Guangzhou 510120, China (e-mail: huanghui765@hotmail.com).
KZ and FH contributed equally to this research.
This work was supported in part by the Science & Technology Star of Zhujiang city project [2011016], Yat-Sen Scholarship for Yong Scientist, NSFC [91029742, 81170647 and 81370837], Fok Ying-Tong Education Foundation for Young Teachers in the Higher Education Institutions of China [132030] and Guangdong Province Key Laboratory of Computational Science at the Sun Yat-sen University [201106007] to Hui Huang.
We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work. We also declare that there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.
KZ and FFH wrote the manuscript. HH and JFW contributed to the design of the individual trials. JC and QQC were responsible for statistical analysis. TW, RZ, and ZYZ were involved in the conduct/data collection and critical analysis, and shared in final responsibility for the content of the manuscript and the decision to submit it for publication.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000130

of overweight and obesity in LVH is still under debate and is not known in hypertensive patients.

The aim of the present meta-analysis was mainly to evaluate the influence of overweight and obesity on LVH regression in hypertensive patients. Furthermore, previous studies have showed that different antihypertensive drugs have different antihypertrophic effect.[9] Variant methods used for BP measurement are of different help to demonstrate the BP variability, which is pivotal for LVH. BP measurement methods such as office or clinic BP measurement and 24-h ambulatory BP monitoring were also found to have a close association with clinical cardiovascular outcomes in hypertensive patients.[10] In addition, the ETODH study showed age is related with the prevalence of severe LVH in essential hypertension.[11] However, the influence of antihypertensive drugs, BP measurement methods, and age on LVH regression in overweight and obese hypertensive patients was not completely clear. So in the present study, we also explored the influence of these factors on LVH regression in overweight and obese patients with hypertension.

METHODS

Selection of Studies

We performed an electronic literature search of PubMed database since 1992 to January, 2013, using the terms ''cardiac hypertrophy,'' ''left ventricular hypertrophy,'' ''LVH,'' ''hypertension,'' ''essential hypertension,'' ''arterial hypertension,'' and ''regression.'' We also searched the reference lists of articles for relevant titles. Selection criteria for inclusion in the meta-analysis were as follows: randomized controlled trials (RCTs) with parallel design; full-text articles published in peer-reviewed journals; English-language publications; follow-up time $\geq$3 months; the age of the patients of all races were older than 19 years; LVM was measured by echocardiography. And left ventricular mass index (LVMI) that was calculated as LVM in grams divided by body surface area in square meters (the studies that normalized LVMI for height$^{2.7}$ were excluded); reporting BMI at baseline; reporting LVMI at baseline and at the end of follow-up time; and all patients evaluated had treated or never-treated essential, nonmalignant hypertension.

Data Extraction and Quality Assessment

Two investigators independently reviewed all potentially eligible studies and the following data were collected: study design, name of the authors, name of the journal, year of the publication, sample size, age, sex ratio, follow-up time, type of drugs, systolic blood pressure (SBP), diastolic blood pressure (DBP), BP measurement methods, BMI, and LVMI at baseline and at the end of follow-up time. Discrepancies were resolved by reviewing the articles again to achieve consensus. Methodological quality was evaluated using the modified Jadad scale.[12] Eight-point scale was designed to assess the included RCTs. Scores of 4 to 8 denoted high quality, and scores of 0 to 3 represented low quality.

Statistical Analysis

Descriptive data of all participants are given the mean and range or median (minimum, maximum). Each RCT was composed of $\geq$2 treatment arms, and each type of treatment was taken as a separate observation, which made possible multivariate adjustments for differences in parameters (such as age, sex, BP, and LVMI at baseline) among BMI classification. Continuous data were analyzed using weighted mean differences (WMDs) and 95% confidence intervals (CIs). We used fixed or random effects model to estimate the differences among groups according to the absence or presence of heterogeneity among studies. Statistical heterogeneity across studies was assessed using I^2 statistic with significance being set at $I^2 > 50\%$. Multivariable weighted metaregression was used to analyze the possible sources of heterogeneity. Unpaired t test and nonparametric test were used for comparisons between or among groups, respectively. Publication bias was evaluated by using funnel plots, Begg test, and Egger test. A 2-tailed $P < 0.05$ was considered significant. Statistical analyses were performed using Stata version 12.0 (Stata Corp, College Station, TX).

RESULTS

Study Selection

A total of 28 RCTs[13–40] with 2403 hypertensive patients were identified for inclusion from 6042 relevant publications. The flow of selecting studies for the meta-analysis was shown in Figure 1.

Baseline Characteristics and Study Quality

Table 1 summarized the baseline characteristics and study quality of the included trials. Sample size of the studies ranged from 24 to 411 participants, totaling 2403 participants.[13–40] The average age ranged from 43.8 to 66.7 years, and men accounted for 23.7% to 100% in each study. The range of mean SBP at baseline was 144 to 189 mmHg, whereas the range of mean DBP was 86 to 106 mmHg. At baseline, the average BMI ranged from 19.5 to 30.5 g/m^2, whereas the echocardiographic hypertrophic indicator, LVMI, ranged from 98.2 to 163.5 g/m^2. Mean follow-up time was 10.4 months (range: 3–48 months), and the study quality score ranged from 3 to 7. Five types of antihypertensive drugs were used in studies: angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), beta-receptor blockers (β-blockers), and diuretics. We grouped the studies

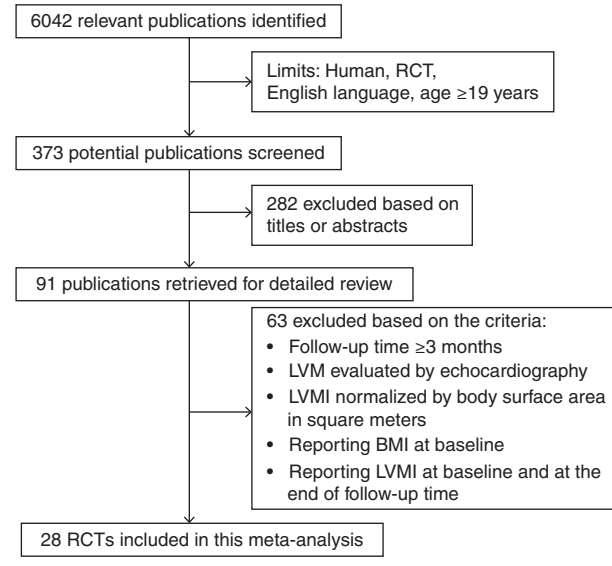

FIGURE 1. Process of study selection. BMI = body mass index, LVM = left ventricular mass, LVMI = left ventricular mass index, RCT = randomized controlled trial.

TABLE 1. Baseline Characteristics and Study Quality of Study Population in 28 Trials (n = 2403)

Author (year)	n	Men, %	Mean Age, y	Mean Follow-up, month	Mean SBP, mmHg	Mean DBP, mmHg	Mean BMI, g/m^2	Mean LVMI, g/m^2	Type of Drugs	Modified Jadad Score
Dahlof and Hansson (1992)[13]	28	100	46	16	155	102	27	125	ACEI, diuretics	4
Jula and Karanko (1994)[14]	76	60.5	43.8	12	147	97	27.4	119	None	4
Diez and Laviades (1994)[15]	87	57.5	47	6	—	—	29	102	ACEI	3
Grandi et al (1995)[16]	36	50	44	6	156	106	24.8	140.5	ACEI, CCB	4
Schobel et al (1996)[17]	43	67.4	52	6	146	94	27.8	145	β-blockers, other	4
Ueno et al (1997)[18]	36	44.4	52	12	173	103	25.2	118.7	ACEI, CCB, other	4.5
Roman et al (1998)[19]	50	74	51.2	6	150	95	27.8	98.2	ACEI, diuretics	4
Agabiti-Rosei et al (1998)[20]	32	56.3	50.4	6	157	101	27.8	141.8	CCB, diuretics	5
Martina and Lau (1999)[21]	25	64	51	4	150	101	30.5	149.5	ARB, CCB	4
Cheung et al (1999)[22]	33	60.6	49.5	3	153	96	25	115.4	ACEI	5
Gosse et al (2000)[23]	411	56.4	54.5	12	172	101	26.8	140.9	ACEI, diuretics	5
Avanza et al (2000)[24]	46	58.7	54	10	172	103	26.7	144.7	ACEI, ARB	4
Novo et al (2001)[25]	46	54.3	55	6	157	104	25.3	140.4	ACEI, β-blockers, diuretics	3
Skudicky et al (2002)[26]	173	23.7	51	4	151	97	30.3	118	ACEI, CCB	4
Cuspidi et al (2002)[27]	196	62.2	53	12	163	101.3	26.2	142.2	ARB, ACEI	7
Takami and Shigematsu (2003)[28]	45	100	61.1	6	174	97	23.1	129.8	CCB	4
Sakata et al (2003)[29]	60	50	62	12	154	90	22.5	124.5	ACEI, CCB	3
Yasunari et al (2004)[30]	104	59.6	63	8	152	93	24.2	163.5	ARB, CCB	7
Rinder et al (2004)[31]	28	82.1	65.9	6	154	91	30.2	118.2	diuretics	4
de Luca et al (2004)[32]	214	64.5	53.5	12	162	99	26.8	127.4	ACEI, β-blockers, diuretics	5
Bilge et al (2005)[33]	27	63	48	6	144	96	26.4	120	ACEI, CCB	3
Anan et al (2005)[34]	31	54.8	59	10	157	97	25.6	151.3	ACEI, ARB	3
Agabiti-Rosei et al (2005)[35]	174	60.3	53.3	48	160	100	27.3	104.9	CCB, β-blockers	5
Grandi et al (2008)[36]	24	79.2	49	6	145	94	28.6	150.5	ACEI, ARB, CCB	3
Takami and Saito (2011)[37]	50	70	66.7	6	152	86	25.8	122.8	ARB, CCB	4
Pan et al (2011)[38]	41	61	64	12	189	101	24.8	129.5	ARB, other	4
Caglar and Dincer (2011)[39]	106	48.1	50.8	10	160	99	29.5	147.4	ACEI, β-blockers	5
Fogari et al (2012)[40]	181	51.4	64	12	147	92	27.2	132.7	ARB, CCB	5

ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers, β-blockers = beta-receptor blockers, BMI = body mass index, CCB = calcium channel blockers, DBP = diastolic blood pressure, LVH = left ventricular hypertrophy, LVMI = left ventricular mass index, SBP = systolic blood pressure.

according to BMI classification of the World Health Organization (WHO) guideline[41]: normal weight (18.5–24.9 kg/m^2) group, overweight (25–29.9 kg/m^2) group, and obesity (≥30 kg/m^2) group. No significant difference in age, SBP, DBP, and LVMI at baseline was found among these 3 groups (Table 2).

LVH Regression in Different BMI Subgroups

Although the LVMI at baseline was consistent among the 3 BMI groups (Table 2), LVMI significantly decreased during the follow-up period: normal-weight group (WMD 13.78 g/m^2, 95% CI [9.06, 18.50], $P < 0.001$), overweight group (WMD 14.27 g/m^2, 95% CI [11.00, 17.54], $P < 0.001$], and obesity

TABLE 2. The Baseline Characteristics Among the 3 Body Mass Index Groups

Baseline	Normal Weight	Overweight	Obesity	*P*
Age, y	60.9 (44–64)	53 (43.5–67.5)	51.5 (47–66.4)	0.13
SBP, mmHg	155.6 (152–174)	155.4 (143–174)	152 (145–154)	0.14
DBP, mmHg	96.8 (90–106)	97 (85.8–106)	98.5 (90–102)	0.63
LVMI, g/m^2	129.9 (120.8–166)	128.2 (92.7–155)	128.2 (118–163)	0.37

Values are expressed as median (minimum, maximum). *P* value showed the comparison of baseline characteristics among 3 body mass index groups. DBP = diastolic blood pressure, LVMI = left ventricular mass index, SBP = systolic blood pressure.

group (WMD 22.05 g/m^2, 95% CI [13.67, 30.44], $P < 0.001$) (Figure 2). The comparison among the 3 groups showed that the regression of LVH was the most obvious in obesity group, followed by overweight group and normal-weight group ($P < 0.001$).

SBP Reduction in Different BMI Subgroups

To explore whether LVMI regression is associated with the degree of SBP reduction, we analyzed SBP reduction in different BMI subgroups. Interestingly, although SBP at baseline showed no difference among the 3 groups (Table 2), SBP significantly reduced in normal-weight group (WMD 24.92 mmHg, 95% CI [16.46, 33.39], $P < 0.001$), followed by overweight group (WMD 20.34 mmHg, 95% CI [17.05, 23.6], $P < 0.001$), and obesity group (WMD 16.68 mmHg, 95% CI [10.79, 22.56], $P < 0.001$) (Figure 3). The comparison of SBP reduction among the 3 BMI subgroups was significant ($P < 0.001$).

DBP Reduction in Different BMI Subgroups

We also analyzed DBP reduction in different BMI subgroups. The results showed that all subgroups had a significant DBP reduction ($P < 0.001$, Figure 4). Both overweight group and obesity group had a larger DBP reduction than normal group ($t = 2.14$, $P = 0.033$; $t = 2.15$, $P = 0.032$, respectively). However, no significant difference was found between overweight group and obesity group ($t = 0.82$, $P = 0.41$).

Different Antihypertensive Drugs and the Regression of LVH in Overweight and Obese Hypertensive Patients

Different antihypertensive drugs exhibited different anti-LVH effect in overweight and obese hypertensive patients. As shown in Figure 5, the regression of LVH was 19.27 g/m^2 (WMD) (95% CI [15.25, 23.29], $P < 0.001$) in the renin–angiotensin system inhibitor (RASI) (ACEI/ARB) group, 17.81 g/m^2 (WMD) (95% CI [6.53, 29.09], $P < 0.001$) in β-blockers subgroup, 13.93 g/m^2 (WMD) (95% CI [9.66, 18.21], $P < 0.001$) in CCB subgroup, 7.94 g/m^2 (WMD) (95% CI [2.75, 13.13], $P < 0.001$) in diuretics subgroup, and 6.90 g/m^2 (WMD) (95% CI [3.30, 10.50], $P < 0.001$) in other treatment subgroup. We found that RASI was the most effective to induce LVH regression in overweight and obese patients with hypertension ($P < 0.01$).

Different BP Measurement Methods and the Regression of LVH in Overweight and Obese Hypertensive Patients

According to the BP measurement methods, we grouped the overweight and obese hypertensive patients into 2 groups: 24-h ambulatory BP monitoring (ABPM) group and office/clinic BP measurement group. More LVH regression was found in 24-h ABPM group comparing with office/clinic BP measurement group (18.56 vs 12.14 g/m^2, $P < 0.001$) (Figure 6). This finding indicated that the degree of BP reduction measured by 24-h ABPM had a closer association with the level of LVH regression.

LVH Regression in Different Age Subgroups of Overweight and Obese Hypertensive Patients

Three age subgroups were divided according to the mean age in overweight and obese hypertensive patients: G1, 40 to 49 years' old; G2, 50 to 59 years' old; and G3, age ≥60 years' old. As shown in Figure 7, all 3 groups had a significant LVH regression: G1 (WMD 13.09 g/m^2, 95% CI [6.96, 19.23.39], $P < 0.001$), G2 (WMD 14.93 g/m^2, 95% CI [10.83, 19.04], $P < 0.001$), and G3 (WMD 12.36 g/m^2, 95% CI [5.98, 18.72], $P < 0.001$). G3 (age ≥60 years' old) group showed a less LVMI regression comparing with the other 2 groups ($P < 0.01$). Furthermore, we explored the changes of SBP and DBP in different age subgroups. It was found that BP decreased most in G3 group, followed by G1 and G2 groups (Table 3). The above results indicated that obesity influenced LVH regression independent of BP reduction in the aged population (age ≥60 years' old).

Determinants for the Heterogeneity Among the Studies

Table 4 gave the results of the multivariable metaregression analysis to identify the potential determinants for statistical heterogeneity among studies. Both BP measurement methods and LVMI at baseline contributed to the statistical heterogeneity (BP measurement methods, $P = 0.017$; LVMI at baseline, $P = 0.023$, Table 4). However, factors like age, follow-up time, sample size, study quality, BP, and type of drugs showed no contributions ($P > 0.05$, Table 4).

Publication Bias

When we explored for potential publication bias, the funnel plot did not appear asymmetrically (Figure 8), and no significant difference was found in the Begg and Egger test (Begg test, $P = 0.38$; Egger test, $P = 0.10$).

DISCUSSION

The main findings of this current meta-analysis were that the regression of LVH during the follow-up time was the most obvious in overweight and obese hypertensive patients. The degree of LVH regression was not in the same ranking order of the BP reduction. RASI was the most effective antihypertensive drug for LVH regression in overweight and obese hypertensive patients. The 24-h ABPM method was more useful to guide BP controlling to reflect LVH regression in overweight and obese hypertensive patients. Furthermore, in overweight and obese hypertensive patients, older age (age ≥60 years) was also an influencing factor for the reduction of LVH.

LVH is a definite cardiac damage in hypertensive patients and associates with a series of cardiovascular events.[2] Overweight and obesity are also important risk factors for cardiovascular diseases such as heart failure and hypertension.[42,43] Thus, if a person simultaneously had overweight/obesity and LVH, the incidence of cardiovascular events will be significantly increased. It was found that overweight and obese hypertensive patients had an absolute LVM 15% to 41% higher than that in a reference normal group of normal-weight normotensive subjects, independent of sex and SBP.[44] In the present study, no difference of LVMI at baseline between overweight/obese patients and normal-weight patients may because there are many factors determinate the LVM such as race, the duration of hypertension, etc.[45,46] Our results showed that after adjustment of the BP and LVMI at baseline, the regression of LVH was the most obvious in overweight and obese hypertensive patients and was not accompanied with the degree of SBP reduction. It suggested that overweight and obesity might be the independent risk factors for LVH. And during the treatment for

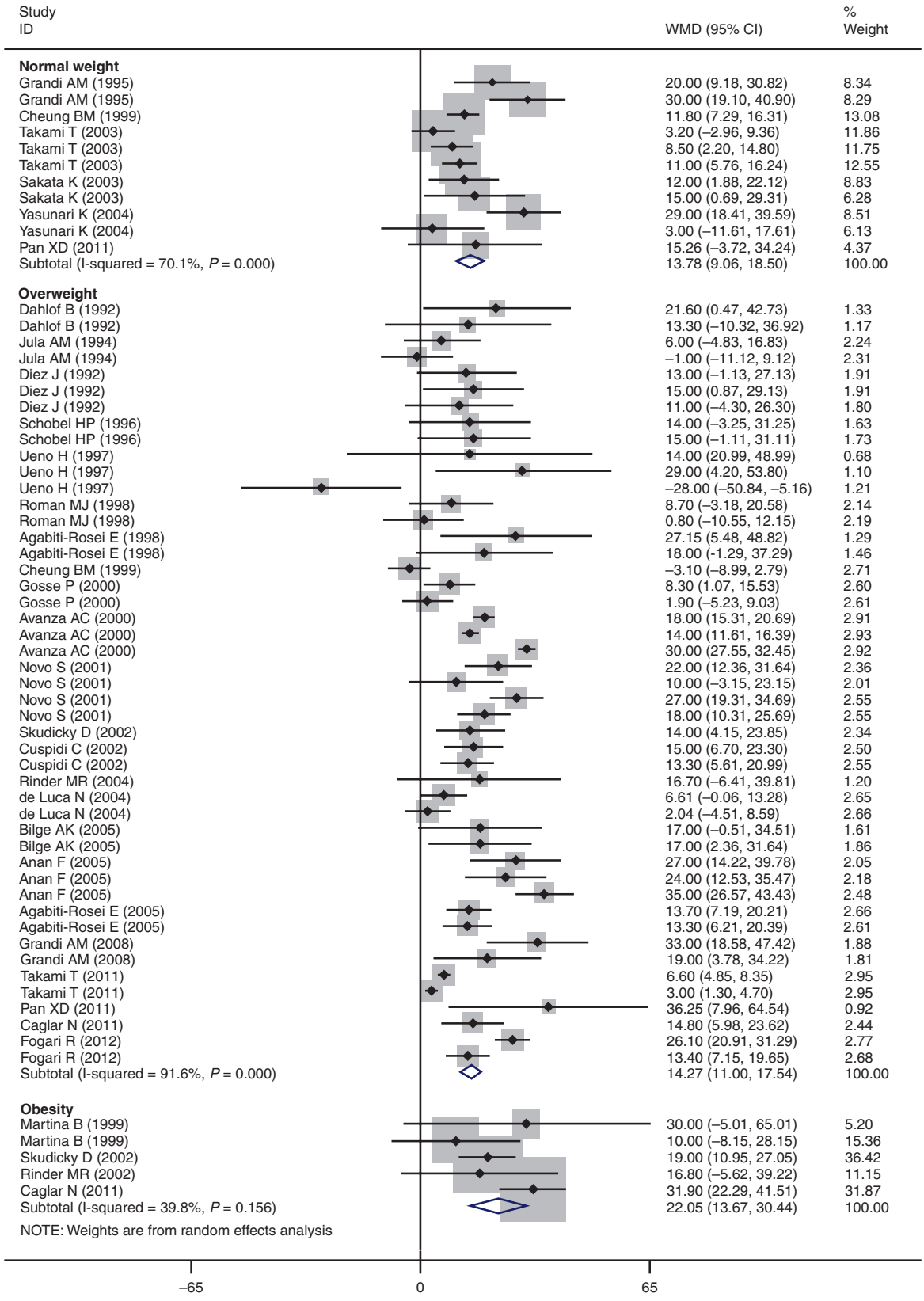

FIGURE 2. LVH regression in different BMI subgroups. BMI = body mass index, CI = confidence interval, LVH = left ventricular hypertrophy, WMD = weighted mean difference.

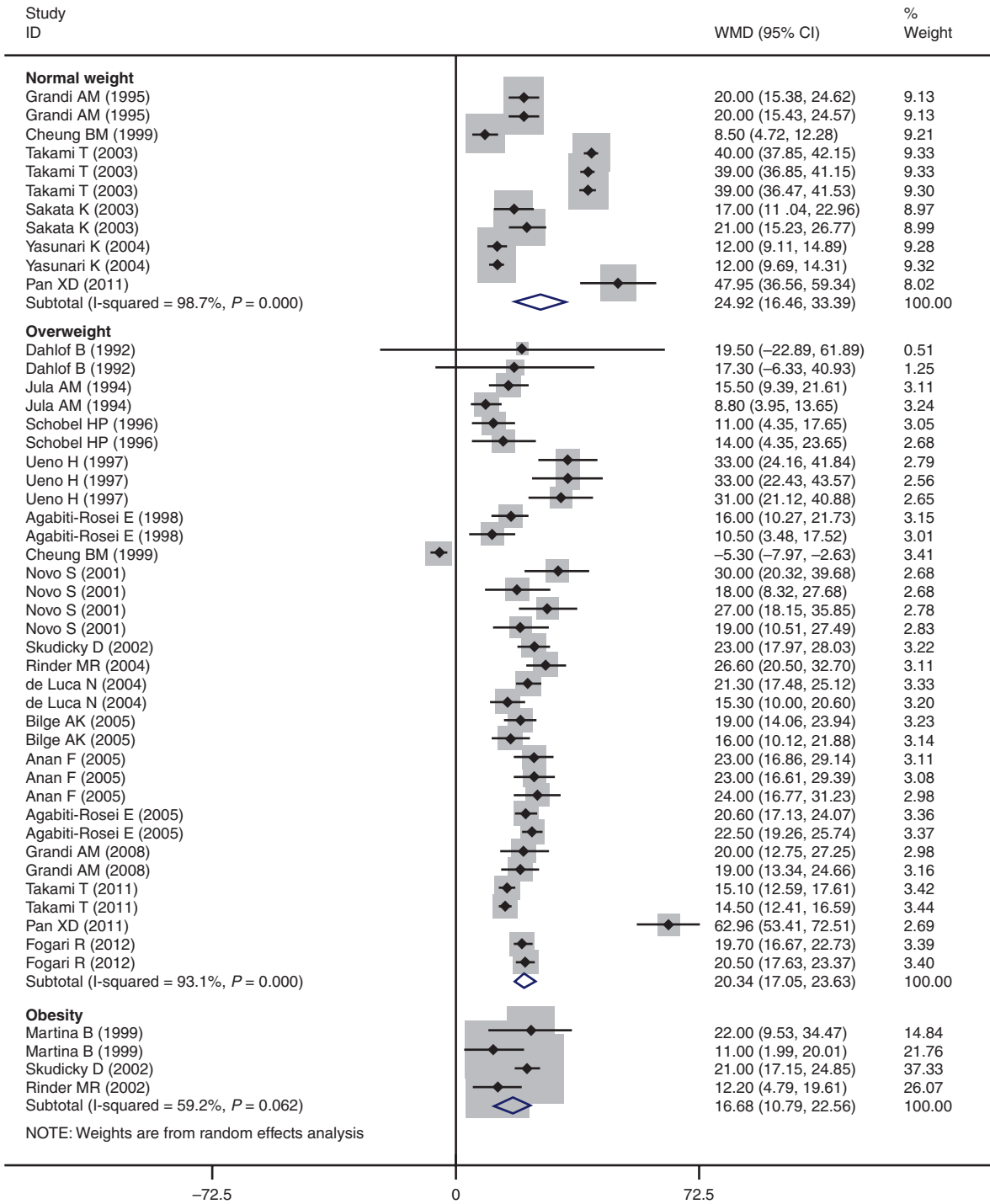

FIGURE 3. SBP reduction in different BMI subgroups. BMI = body mass index, CI = confidence interval, SBP = systolic blood pressure, WMD = weighted mean difference.

regression of LVH, we should pay more attention to the body weight control. However, to what extent an increase in LVM directly resulting from overweight and obesity is unclear. We observed that SBP reduction was less in overweight and obese hypertensive patients, whereas the reduction of DBP was higher in overweight and obese hypertensive patients. This discrepancy may indicate that DBP reduction contributes more to the regression of LVH.[12] Overweight and obesity are conditions of increased adipose tissue mass. An excess of body fat requires a high cardiac output to meet the metabolic demand. When this hemodynamic burden is sustained, LVH will form.[47] Insulin resistance is considered to be another important

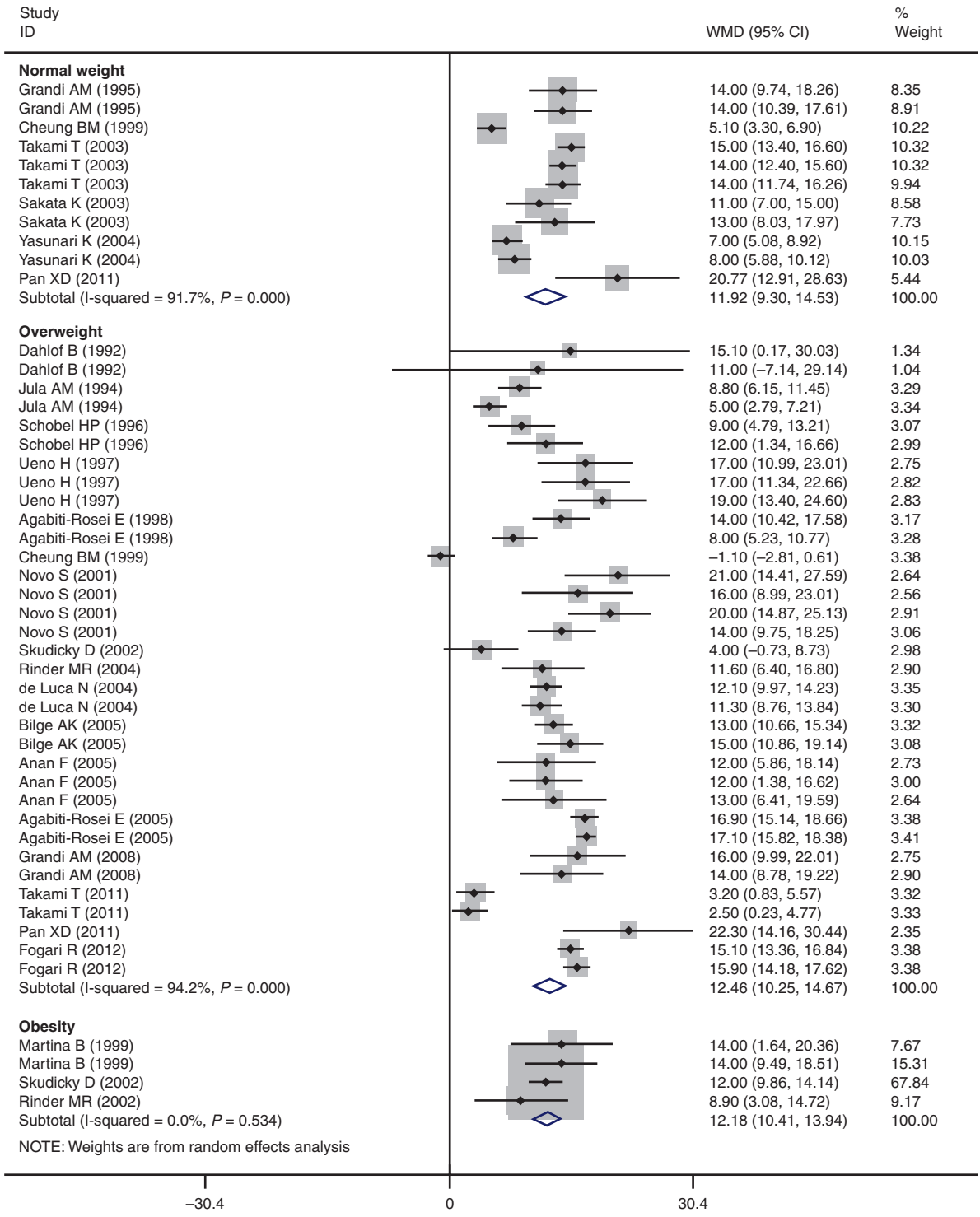

FIGURE 4. DBP reduction in different BMI subgroups. BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, WMD = weighted mean difference.

determinant for LVH in overweight and obese patients. It can lead to LVH through its growth-stimulating effect, increased sodium reabsorption in kidney, etc.[48] Both obesity and insulin resistance are the characteristics of metabolic syndrome (MetS). A previous study showed that BMI, but not the age and SBP, is the driving factor behind MetS-related LVM increase.[49] Furthermore, other risk factors such as neurohormonal activation[50] and increased inflammatory cytokines[51] are all reported to be involved in the process of LVH in obesity. However, the dominant mechanism is still unknown.

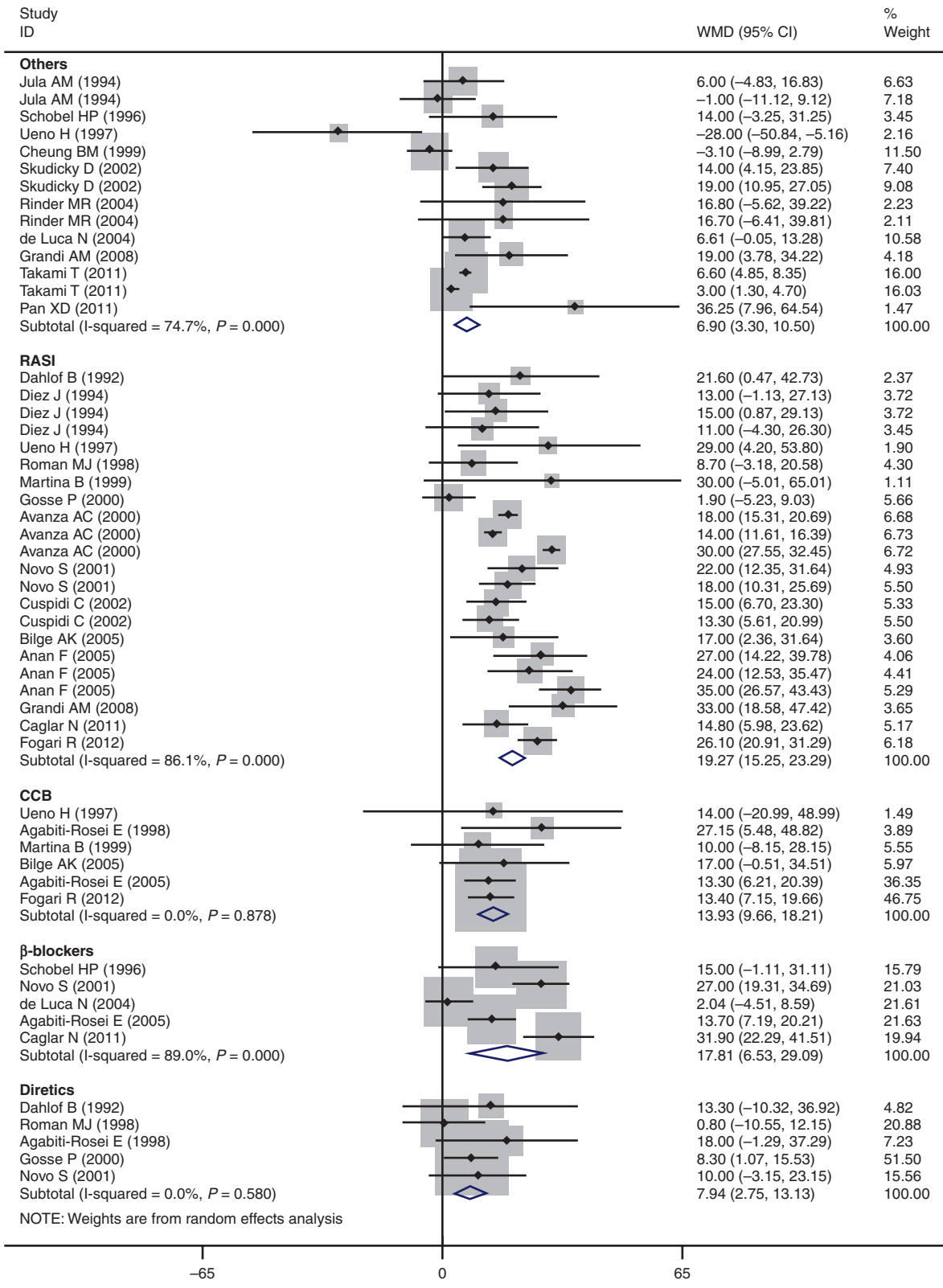

FIGURE 5. Different antihypertensive drugs and the regression of LVH in overweight and obese hypertensive patients. β-blockers = beta-receptor blockers, CCB = calcium channel blockers, CI = confidence interval, LVH = left ventricular hypertrophy, RASI = renin-angiotensin system inhibitor, WMD = weighted mean difference.

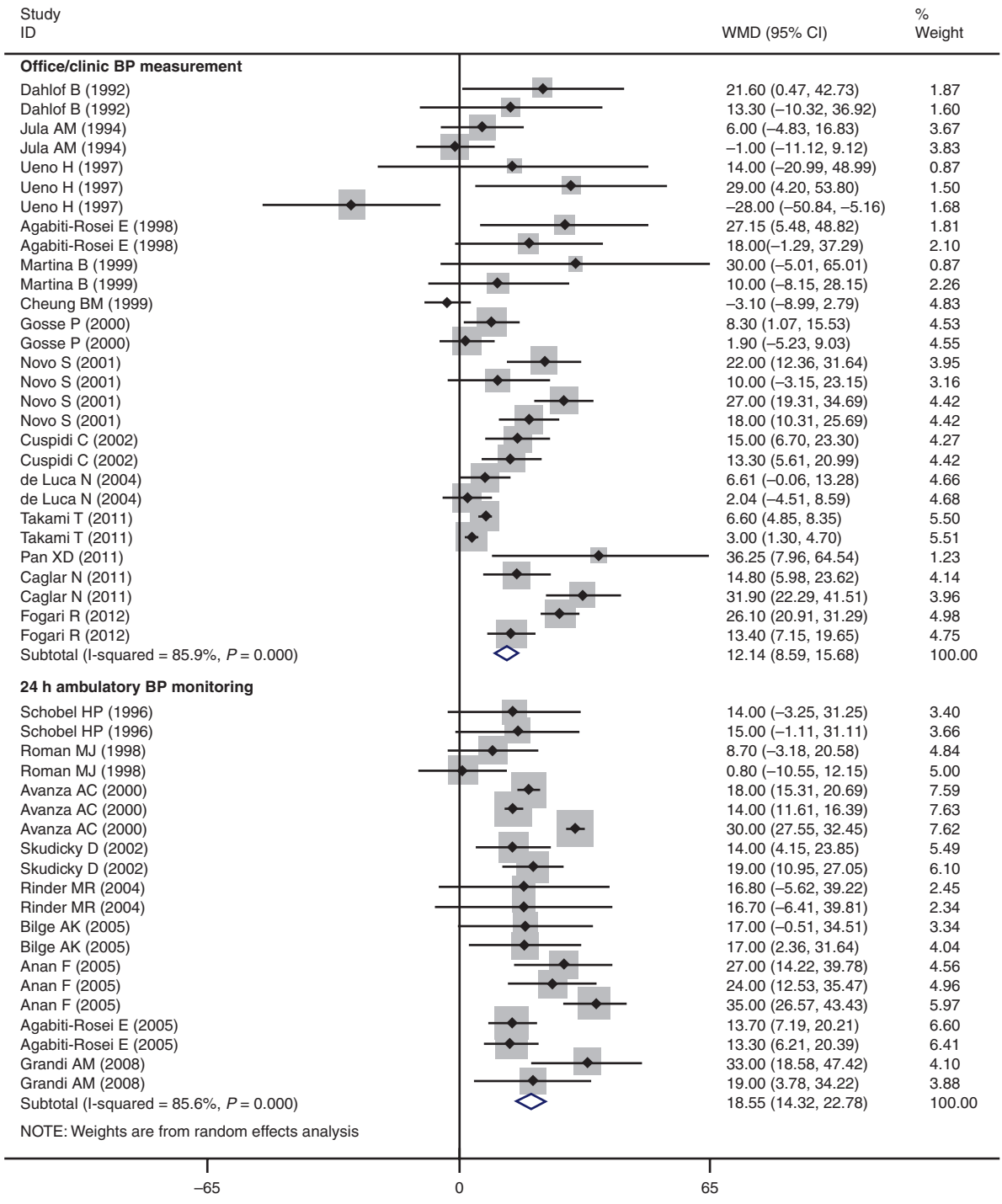

FIGURE 6. Different BP measurement methods and the regression of LVH in overweight and obese hypertensive patients. BP = blood pressure, CI = confidence interval, LVH = left ventricular hypertrophy, WMD = weighted mean difference.

The benefit effect of antihypertensive drugs for LVH regression has been studied extensively. It was found that different antihypertensive drugs had different antihypertrophic effect.[9,52] As for overweight and obese hypertensive patients, there is still a lack of guideline for treating LVH. In the present study, we found that RASI was the most effective antihypertensive drug for regressing LVH in overweight and obese hypertensive patients, which is consistent with recent viewpoints that RASI is considered to be the most appropriate drugs for antihypertensive treatment of obese patients for their possible benefit that they unlikely worsen glucose or lipid metabolism.[53] Activation of the renin–angiotensin system

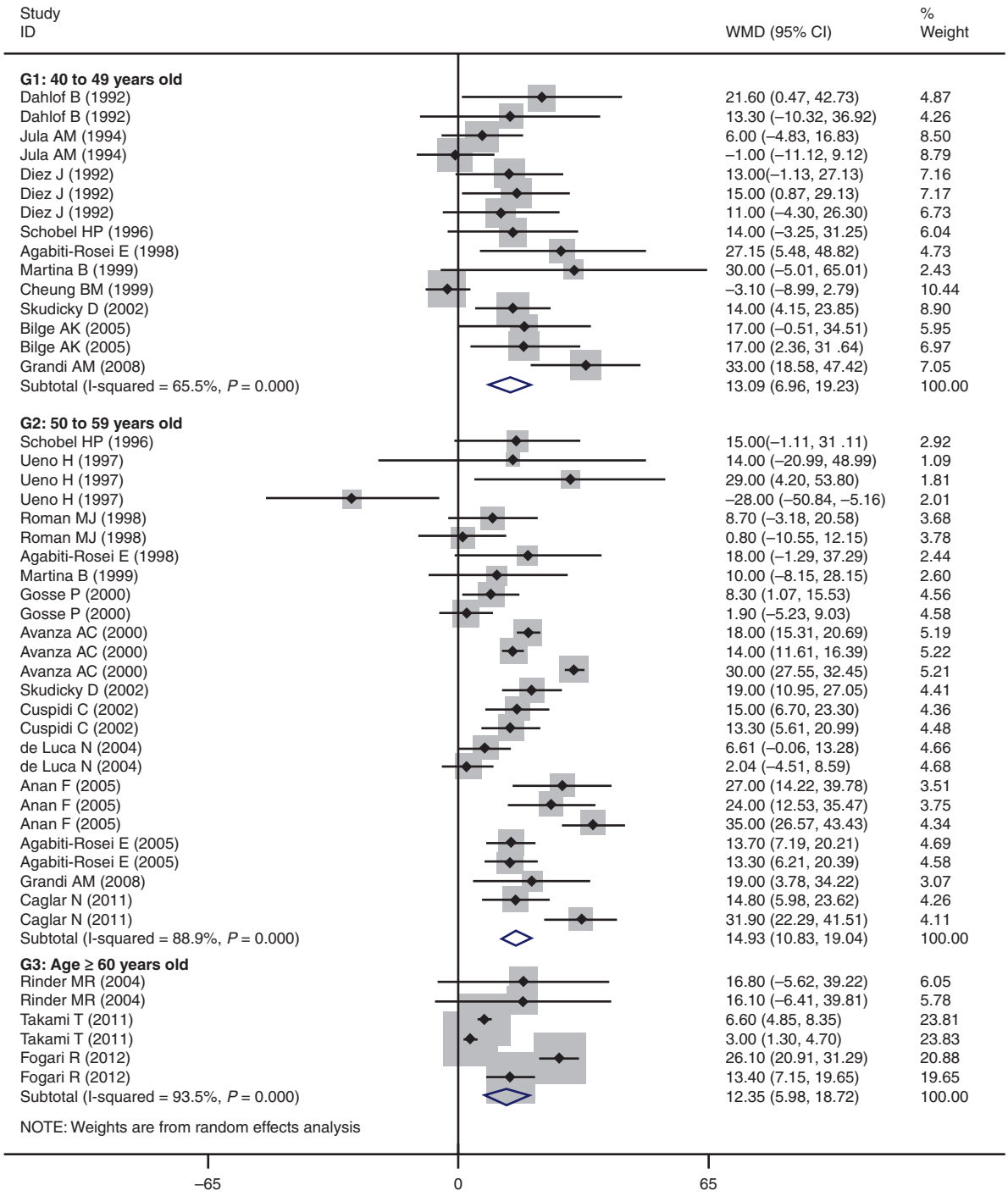

FIGURE 7. LVH regression in different age subgroups of overweight and obese hypertensive patients. CI = confidence interval, LVH = left ventricular hypertrophy, WMD = weighted mean difference.

(RAS) is commonly observed in patients with obesity and the levels of angiotensin II (Ang II) and aldosterone are increased in obese patients,[54–56] so RASI may partly reverse LVH through decreasing the improper activation of RAS. Furthermore, RASI may improve LVH by inhibiting the obesity-induced insulin resistance, because RASI can improve the insulin sensitivity in obese patients.[57,58] As for other antihypertensive drugs, although we found they also had an effect on LVH regression, there is still a lack of sufficient evidence to suggest that they have an affirmative effect for LVH regression in overweight and obese hypertensive patients. More studies are needed to explore this issue.

In addition, we found in this study that in overweight and obese hypertensive patients, the 24-h ABPM group had a greater

TABLE 3. The Reduction of SBP and DBP in Different Age Subgroups of Overweight and Obese Hypertensive Patients

	SBP, mmHg	DBP, mmHg
G1	19.97 (14.80–21.14)	9.54 (4.02–15.06)
G2	14.62 (17.35–21.90)	9.85 (5.87–13.82)
G3	22.12 (19.78–24.46)	13.68 (11.88–15.47)

G1, 40–49 years' old; G2, 50–59 years' old, and G3, age ≥60 years. DBP = diastolic blood pressure, SBP = systolic blood pressure.

LVH regression. There are several BP measurement methods such as office or clinic BP measurement and 24-h ABPM. Previous studies have shown that ABPM had a stronger relationship with morbid or fatal events than office BP measurement and was a more sensitive risk predictor of clinical cardiovascular outcomes than office BP.[10,59,60] Our study further demonstrated that in overweight and obese hypertensive patients, ABPM was also associated with the target organs' damage, for example LVH. Because of the limitation of the data on the publications, we only analyzed this at baseline. However, 24-h ABPM may provide a more reliable measurement for actual BP burden in overweight and obese hypertensive patients. Furthermore, we found significant regression of LVH in different age subgroups, implying that even in older overweight and obese hypertensive patients, as long as the strategy is appropriate, LVH can also be regressed. However, at the same time, we found that the older age (≥60 years) influenced the degree of LVH regression in overweight and obese hypertensive patients after adjustment for SBP and DBP reduction. The possible explanation may be because the arterial stiffness is more severe in overweight and obese elderly patients.[61] However, there are other studies showing that obesity is associated with LVH independent of age.[49] And when compare the influence of age, the effects of antihypertensive therapies cannot be overlooked. So more studies are needed to clarify this issue.

TABLE 4. Determinants of the Statistical Heterogeneity in Multivariable Metaregression Analysis

Variable	Partial Regression Coefficient	*P*
Age, y	1.25	0.22
Follow-up time, min	0.78	0.44
Sample size	0.51	0.62
Study quality	−1.11	0.27
BP measurement methods[#]	−2.50	0.017
SBP at baseline, mmHg	−1.97	0.056
DBP at baseline, mmHg	1.35	0.19
LVMI at baseline, g/m^2	3.72	0.001
Type of drugs[*]	−0.68	0.50

BP = blood pressure, DBP = diastolic blood pressure, LVMI = left ventricular mass index, SBP = systolic blood pressure.

[*] Classified based on the drugs used in study (angiotensin-converting enzyme inhibitors [ACEI], angiotensin receptor blockers [ARB], calcium channel blockers [CCB], beta-receptor blockers, diuretics, and others).

[#] BP measurement methods including 24-h ambulatory BP monitoring (ABPM) method and office/clinic BP measurement method.

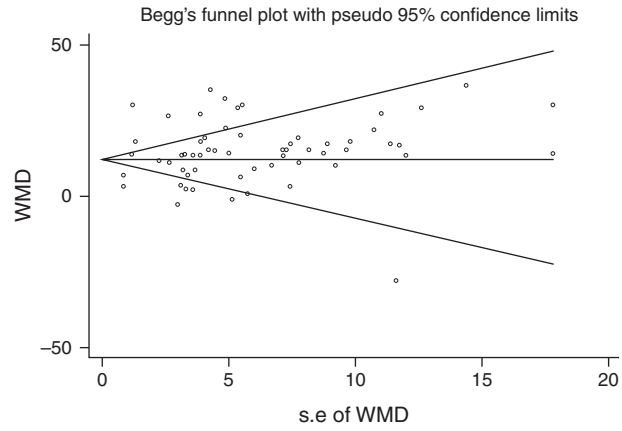

FIGURE 8. Begg funnel plot for publication bias. WMD = weighted mean difference.

Study Limitations

Some limitations of our meta-analysis may restrict the interpretation of results. First, the characteristics among included studies are different, such as the ratio of gender, follow-up time, and drugs used. Inconsistency of these factors may influence the results to some degree. To explore the influence of the above factors, better designed RCTs are required. Second, there are insufficient data on race, dietary salt intake, and pulse wave for a reliable stratified analysis in this study. Third, we only enrolled the studies that evaluated LVH by echocardiography and LVMI was calculated as LVM in grams divided by body surface area in square meters. Whether data from studies evaluating LVH by magnetic resonance imaging and electrocardiogram or by echocardiography but LVMI normalized by height$^{2.7}$ will show similar findings to our results needs further exploring. Fourth, our study is a 'post-hoc' categorization of the studies; other analyzed ways, such as those according to prespecified inclusion criteria, should be used in future studies.

In summary, we found that overweight and obesity were associated with LVH independent of BP. RASI was the most effective antihypertensive drug for regressing LVH in overweight and obese hypertensive patients. Monitoring 24-h ABPM may effectively help to evaluate the LVH in overweight and obese hypertensive patients. Antihypertensive treatment at early age could make the overweight and obese hypertensive patients benefit more for LVH regression.

REFERENCES

1. Allison DB, Fontaine KR, Manson JE, et al. Annual deaths attributable to obesity in the United States. *JAMA.* 1999;282:1530–1538.

2. Schillaci G, Verdecchia P, Porcellati C, et al. Continuous relation between left ventricular mass and cardiovascular risk in essential hypertension. *Hypertension.* 2000;35:580–586.

3. Reisin E, Jack AV. Obesity and hypertension: mechanisms, cardiorenal consequences, and therapeutic approaches. *Med Clin North Am.* 2009;93:733–751.

4. Ballo P, Motto A, Mondillo S, et al. Impact of obesity on left ventricular mass and function in subjects with chronic volume overload. *Obesity (Silver Spring).* 2007;15:2019–2026.

5. Jhaveri RR, Pond KK, Hauser TH, et al. Cardiac remodeling after substantial weight loss: a prospective cardiac magnetic resonance study after bariatric surgery. *Surg Obes Relat Dis.* 2009;5:648–652.
6. Haufe S, Utz W, Engeli S, et al. Left ventricular mass and function with reduced-fat or reduced-carbohydrate hypocaloric diets in overweight and obese subjects. *Hypertension.* 2012;59:70–75.
7. Hsuan CF, Huang CK, Lin JW, et al. The effect of surgical weight reduction on left ventricular structure and function in severe obesity. *Obesity (Silver Spring).* 2010;18:1188–1193.
8. Barouch LA. Disruption of leptin signaling contributes to cardiac hypertrophy independently of body weight in mice. *Circulation.* 2003;108:754–759.
9. Fagard RH, Celis H, Thijs L, et al. Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies. *Hypertension.* 2009;54:1084–1091.
10. Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension.* 2005;46:156–161.
11. Cuspidi C, Meani S, Sala C, et al. Age related prevalence of severe left ventricular hypertrophy in essential hypertension: echocardiographic findings from the ETODH study. *Blood Press.* 2012;21:139–145.
12. Zhang K, Chen J, Liu Y, et al. Diastolic blood pressure reduction contributes more to the regression of left ventricular hypertrophy: a meta-analysis of randomized controlled trials. *J Hum Hypertens.* 2013;27:698–706.
13. Dahlof B, Hansson L. Regression of left ventricular hypertrophy in previously untreated essential hypertension: different effects of enalapril and hydrochlorothiazide. *J Hypertens.* 1992;10:1513–1524.
14. Jula AM, Karanko HM. Effects on left ventricular hypertrophy of long-term nonpharmacological treatment with sodium restriction in mild-to-moderate essential hypertension. *Circulation.* 1994;89:1023–1031.
15. Diez J, Laviades C. Insulin-like growth factor-1 and cardiac mass in essential hypertension: comparative effects of captopril, lisinopril and quinapril. *J Hypertens Suppl.* 1994;12:S31–S36.
16. Grandi AM, Bignotti M, Gaudio G, et al. Ambulatory blood pressure and left ventricular changes during antihypertensive treatment: perindopril versus isradipine. *J Cardiovasc Pharmacol.* 1995;26:737–741.
17. Schobel HP, Langenfeld M, Gatzka C, et al. Treatment and post-treatment effects of alpha- versus beta-receptor blockers on left ventricular structure and function in essential hypertension. *Am Heart J.* 1996;132:1004–1009.
18. Ueno H, Takata M, Tomita S, et al. The effects of long-term treatment on left ventricular hypertrophy in patients with essential hypertension: relation to changes in neurohumoral factors. *J Cardiovasc Pharmacol.* 1997;30:643–648.
19. Roman MJ, Alderman MH, Pickering TG, et al. Differential effects of angiotensin converting enzyme inhibition and diuretic therapy on reductions in ambulatory blood pressure, left ventricular mass, and vascular hypertrophy. *Am J Hypertens.* 1998;11:387–396.
20. Agabiti-Rosei E, Zulli R, Muiesan ML, et al. Reduction of cardiovascular structural changes by nifedipine GITS in essential hypertensive patients. *Blood Press.* 1998;7:160–169.
21. Martina B, Dieterle T, Weinbacher M, et al. Effects of losartan titrated to Losartan/Hydrochlorothiazide and amlodipine on left ventricular mass in patients with mild-to-moderate hypertension. A double-blind randomized controlled study. *Cardiology.* 1999;92:110–114.
22. Cheung BM, Lau CP. Fosinopril reduces left ventricular mass in untreated hypertensive patients: a controlled trial. *Br J Clin Pharmacol.* 1999;47:179–187.
23. Gosse P, Sheridan DJ, Zannad F, et al. Regression of left ventricular hypertrophy in hypertensive patients treated with indapamide SR 1.5 mg versus enalapril 20 mg: the LIVE study. *J Hypertens.* 2000;18:1465–1475.
24. Avanza AC Jr, El Aouar LM, Mill JG. Reduction in left ventricular hypertrophy in hypertensive patients treated with enalapril, losartan or the combination of enalapril and losartan. *Arq Bras Cardiol.* 2000;74:103–117.
25. Novo S, Abrignani MG, Novo G, et al. Effects of drug therapy on cardiac arrhythmias and ischemia in hypertensives with LVH. *Am J Hypertens.* 2001;14:637–643.
26. Skudicky D, Sareli P, Libhaber E, et al. Relationship between treatment-induced changes in left ventricular mass and blood pressure in black african hypertensive patients: results of the Baragwanath Trial. *Circulation.* 2002;105:830–836.
27. Cuspidi C, Muiesan ML, Valagussa L, et al. Comparative effects of candesartan and enalapril on left ventricular hypertrophy in patients with essential hypertension: the candesartan assessment in the treatment of cardiac hypertrophy (CATCH) study. *J Hypertens.* 2002;20:2293–2300.
28. Takami T, Shigematsu M. Effects of calcium channel antagonists on left ventricular hypertrophy and diastolic function in patients with essential hypertension. *Clin Exp Hypertens.* 2003;25:525–535.
29. Sakata K, Yoshida H, Tamekiyo H, et al. Comparative effect of clinidipine and quinapril on left ventricular mass in mild essential hypertension. *Drugs Exp Clin Res.* 2003;29:117–123.
30. Yasunari K, Maeda K, Watanabe T, et al. Comparative effects of valsartan versus amlodipine on left ventricular mass and reactive oxygen species formation by monocytes in hypertensive patients with left ventricular hypertrophy. *J Am Coll Cardiol.* 2004;43:2116–2123.
31. Rinder MR, Spina RJ, Peterson LR, et al. Comparison of effects of exercise and diuretic on left ventricular geometry, mass, and insulin resistance in older hypertensive adults. *Am J Physiol Regul Integr Comp Physiol.* 2004;287:R360–368.
32. de Luca N, Mallion JM, O'Rourke MF, et al. Regression of left ventricular mass in hypertensive patients treated with perindopril/indapamide as a first-line combination: the REASON echocardiography study. *Am J Hypertens.* 2004;17:660–667.
33. Bilge AK, Atilgan D, Tukek T, et al. Effects of amlodipine and fosinopril on heart rate variability and left ventricular mass in mild-to-moderate essential hypertension. *Int J Clin Pract.* 2005;59:306–310.
34. Anan F, Takahashi N, Ooie T, et al. Effects of valsartan and perindopril combination therapy on left ventricular hypertrophy and aortic arterial stiffness in patients with essential hypertension. *Eur J Clin Pharmacol.* 2005;61:353–359.
35. Agabiti-Rosei E, Trimarco B, Muiesan ML, et al. Cardiac structural and functional changes during long-term antihypertensive treatment with lacidipine and atenolol in the European Lacidipine Study on Atherosclerosis (ELSA). *J Hypertens.* 2005;23:1091–1098.
36. Grandi AM, Solbiati F, Laurita E, et al. Effects of dual blockade of renin-angiotensin system on concentric left ventricular hypertrophy in essential hypertension: a randomized, controlled pilot study. *Am J Hypertens.* 2008;21:231–237.
37. Takami T, Saito Y. Effects of Azelnidipine plus OlmesaRTAn versus amlodipine plus olmesartan on central blood pressure and left ventricular mass index: the AORTA study. *Vasc Health Risk Manag.* 2011;7:383–390.

38. Pan XD, Zeng ZH, Liang LY, et al. The effects of simvastatin on left ventricular hypertrophy and left ventricular function in patients with essential hypertension. *Clin Exp Hypertens.* 2011;33:558–564.
39. Caglar N, Dincer I. Comparison between nebivolol and ramipril in patients with hypertension and left ventricular hypertrophy: a randomized open blinded end-point (PROBE) trial. *Eur Rev Med Pharmacol Sci.* 2011;15:1359–1368.
40. Fogari R, Mugellini A, Destro M, et al. Losartan and amlodipine on myocardial structure and function: a prospective, randomized, clinical trial. *Diabet Med.* 2012;29:24–31.
41. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser.* 2000;894:1–253.
42. Kannel WB, Brand N, Skinner JJ Jr et al. The relation of adiposity to blood pressure and development of hypertension. The Framingham study. *Ann Intern Med.* 1967;67:48–59.
43. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med.* 2002;347:305–313.
44. Palmieri V, de Simone G, Arnett DK, et al. Relation of various degrees of body mass index in patients with systemic hypertension to left ventricular mass, cardiac output, and peripheral resistance (The Hypertension Genetic Epidemiology Network Study). *Am J Cardiol.* 2001;88:1163–1168.
45. Pruette CS, Fivush BA, Flynn JT, et al. Effects of obesity and race on left ventricular geometry in hypertensive children. *Pediatr Nephrol.* 2013;28:2015–2022.
46. Barron AJ, Hughes AD, Sharp A, et al. Long-term antihypertensive treatment fails to improve E/e' despite regression of left ventricular mass: an Anglo-Scandinavian cardiac outcomes trial substudy. *Hypertension.* 2014;63:252–258.
47. Ku CS, Lin SL, Wang DJ, et al. Left ventricular filling in young normotensive obese adults. *Am J Cardiol.* 1994;73:613–615.
48. Sasson Z, Rasooly Y, Bhesania T, et al. Insulin resistance is an important determinant of left ventricular mass in the obese. *Circulation.* 1993;88:1431–1436.
49. Federici M, Guerra F, Mancinelli L, et al. The association of left ventricular hypertrophy with metabolic syndrome is dependent on body mass index in hypertensive overweight or obese patients. *PLoS One.* 2011;6:e16630.
50. Engeli S, Sharma AM. The renin-angiotensin system and natriuretic peptides in obesity-associated hypertension. *J Mol Med (Berl).* 2001;79:21–29.
51. Esposito K, Pontillo A, Di Palo C, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA.* 2003;289:1799–1804.
52. Klingbeil AU, Schneider M, Martus P, et al. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med.* 2003;115:41–46.
53. Jordan J, Yumuk V, Schlaich M, et al. Joint statement of the European Association for the Study of Obesity and the European Society of Hypertension: obesity and difficult to treat arterial hypertension. *J Hypertens.* 2012;30:1047–1055.
54. Yasue S, Ebihara K, Nakao K. [Adipose tissue renin-angiotensin system in obese]. *Nihon Rinsho.* 2012;70:1550–1555.
55. Ruster C, Wolf G. The role of the renin-angiotensin-aldosterone system in obesity-related renal diseases. *Semin Nephrol.* 2013;33:44–53.
56. Sarzani R, Guerra F, Mancinelli L, et al. Plasma aldosterone is increased in class 2 and 3 obese essential hypertensive patients despite drug treatment. *Am J Hypertens.* 2012;25:818–826.
57. Brook RD, Bard RL, Kehrer C, et al. Valsartan improves insulin sensitivity without altering vascular function in healthy overweight adults without the metabolic syndrome. *Metab Syndr Relat Disord.* 2007;5:255–261.
58. Marinik EL, Frisard MI, Hulver MW, et al. Angiotensin II receptor blockade and insulin sensitivity in overweight and obese adults with elevated blood pressure. *Ther Adv Cardiovasc Dis.* 2013;7:11–20.
59. Boggia J, Li Y, Thijs L, et al. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. *Lancet.* 2007;370:1219–1229.
60. Clement DL, De Buyzere ML, De Bacquer DA, et al. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med.* 2003;348:2407–2415.
61. Wildman RP, Mackey RH, Bostom A, et al. Measures of obesity are associated with vascular stiffness in young and older adults. *Hypertension.* 2003;42:468–473.

