Achieving a Systolic Blood Pressure Below 130 mmHg Reduces the Incidence of Cardiovascular Events in Hypertensive Patients with Echocardiographic Left Ventricular Hypertrophy

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The Authors declare that there is no conflict of interest.
Running title: SBP below 130 mmHg does not increase CV risk in LVH patients

Abbreviations:
BMI: body mass index
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
CV: cardiovascular
DBP: diastolic blood pressure
ECG-LVH: electrocardiographic left ventricular hypertrophy
Echo-LVH: echocardiographic left ventricular hypertrophy
IQR: interquartile range
LV: left ventricular
LVH: left ventricular hypertrophy
SBP: systolic blood pressure
Abstract

**Background:** Recent reports have evidenced an increased mortality rate in hypertensive patients with electrocardiographic left ventricular hypertrophy (ECG-LVH) achieving systolic blood pressure (SBP) <130mmHg. However, to the best of our knowledge, the actual effects of BP reduction to the ≤130/80mmHg target on the incidence of cardiovascular events in hypertensive patients with a diagnosis of LVH based on echocardiographic-criteria (Echo-LVH) have never been determined. **Methods:** In order to fill this long-standing knowledge gap, we harnessed a population of 9511 hypertensive patients, followed-up for 33.6 [IQR 7.9-72.7] months. The population was divided into six groups according to the average SBP achieved during the follow-up (≤130, 130-to-139, and ≥140mmHg) and absence/presence of Echo-LVH. The primary endpoint was a composite of fatal or non-fatal myocardial infarction and stroke, sudden cardiac death, heart failure requiring hospitalization, revascularization, and carotid stenting. Secondary endpoints included atrial fibrillation and transient ischemic attack. **Results:** During the follow-up, achieved SBP and diastolic BP (DBP) were comparable between patients with and without Echo-LVH. Strikingly, the rate of primary and secondary endpoints was significantly higher in patients with Echo-LVH and SBP>130mmHg, reaching the highest rate in the Echo-LVH group with SBP≥140mmHg. By separate Cox multivariable regressions, after adjusting for potential confounders, both primary and secondary endpoints were significantly associated with SBP≥140mmHg and Echo-LVH. Instead, DBP reduction ≤80mmHg was associated with a significant increased rate of secondary events. **Conclusions:** In hypertensive patients with Echo-LVH, achieving an average in-treatment SBP target ≤130mmHg has a beneficial prognostic impact on incidence of cardiovascular events.

**Key words:** Arterial hypertension; Blood pressure targets; Echocardiography; Left ventricular Hypertrophy
Significance statement

In contrast with recent reports, achieving in-treatment SBP≤130mmHg reduces the incidence of CV events in hypertensive patients with Echo-LVH. Reducing DBP≤80mmHg is instead associated with a higher rate of CV complications. By Cox multivariable regression models, adjusting for potential confounders, the rate of hard and soft CV events was significantly associated with Echo-LVH and SBP≥140mmHg.

Our data indicate that therapeutic strategies in patients with Echo-LVH should aim at reducing SBP≤130mmHg paying attention to not reducing DBP≤80mmHg.
Introduction

The identification of the ideal systolic blood pressure (SBP) target in the most recent guidelines on arterial hypertension (de Boer et al., 2017; Whelton et al., 2018; Williams et al., 2018) has been affected by the results of the SPRINT trial demonstrating that targeting self-measured SBP to <120 mmHg, compared to <140 mmHg, ensued lower rates of non-fatal and fatal major cardiovascular (CV) events (Wright et al., 2015). However, scarce attention has been given to the presence of cardiac damage triggered by the hypertensive disease, which characterizes a common subset of hypertensive patients (Dahlof et al., 2002; Okin et al., 2012). Indeed, the prevalence of left ventricular (LV) hypertrophy (LVH) in middle-aged hypertensive patients is ~40% when diagnosed via echocardiography (Echo-LVH) (Mancia et al., 2022).

Okin and co-workers (Okin et al., 2012) have reported an increased mortality rate with in-treatment SBP <130 mmHg in the population of the “Losartan Intervention for End Point Reduction” (LIFE) study, which included patients with hypertension and electrocardiographic LVH (ECG-LVH). Similarly, more recently, Heimark and colleagues have investigated whether an average achieved SBP <130 mmHg could produce harm in hypertensive patients with ECG-LVH in the “Valsartan Antihypertensive Long-Term Use Evaluation” (VALUE) trial. They observed that whilst hypertensive patients without ECG-LVH achieving average SBP <130 mmHg had a markedly reduced incidence of CV endpoints, those with ECG-LVH achieving average SBP <130 mmHg exhibited instead a higher mortality (Heimark et al., 2023). Based on these findings, the Authors concluded that reaching an average SBP <130 mmHg could prevent CV events in high-risk patients with hypertension but without ECG-LVH, but the same SBP target may be harmful and should be avoided in hypertensive patients with ECG-LVH. In addition, they suggested that, at least until additional detailed information on the BP target in patients with Echo-LVH would have been available, caution should be used in treating patients with hypertension and LVH to SBP targets <130 mmHg (Heimark et al., 2023).
On these grounds, it seems particularly relevant to evaluate what actually happens in hypertensive patients with Echo-LVH when they achieve a target SBP <130 mmHg, in order to avoid that such caution may deprive these high-risk patients of the benefits demonstrated in the SPRINT study. Therefore, we planned to analyze this important issue in the hypertensive patients of our “Campania Salute Network”, a wide population of patients with a high CV risk, well characterized from the CV and from the metabolic point of view, and presenting a long-term follow-up (Izzo et al., 2011; Casalnuovo et al., 2012; Izzo et al., 2015a; Ciccarelli et al., 2017; Mancusi et al., 2022; Trimarco et al., 2023a). Analyses were performed using a composite of major CV events at the time of their first presentation.

Materials and Methods

Population

The Campania Salute Network Registry represents an open electronic registry, characterized by networking to the Hypertension Research Center of the “Federico II” University Hospital in Naples both general practitioners and community hospital-based hypertension clinics. The database generation of the Campania Salute Network was formally approved by the “Federico II” University Hospital Ethic Committee (Izzo et al., 2011; Mancusi et al., 2022; Manzi et al., 2022; Trimarco et al., 2023c). All participants signed a written informed consent for the use of their clinical data for scientific aims (ClinicalTrials.gov Identifier: NCT02211365). The registry includes more than 15000 hypertensive patients; we have previously described the characteristics of this population (Trimarco et al., 2023a). Recruited patients are referred to the Hypertension Research Center of the “Federico II” University Hospital for diagnosis and management (Trimarco et al., 2022). For this study, hypertensive individuals were screened on the basis of the following inclusion criteria:

1. Age ≥18 years;
2. Available follow-up >6 months;
3. No prevalent coronary/cerebrovascular disease and atrial fibrillation;
4. No prevalent valvular heart disease;

5. Available baseline echocardiography with adequate image quality.

We excluded patients harboring health issues that may reduce life expectancy, including dementia, cancer, peripheral vascular disease, abdominal aortic aneurysm, and venous thrombosis (deep vein thrombosis and/or pulmonary embolism). Follow-up time was defined as time from enrollment until incident CV death, or CV event, or end of follow-up, whichever came first.

CV risk factors assessment

Demographics and relevant risk factors were obtained at baseline (enrollment visit), including age, race, sex, stroke history, heart attack history, diabetes mellitus, and smoking habit. Height and body weight were measured to calculate body mass index (BMI). Obesity was defined as a BMI ≥30 kg/m². The clinical examination was done during the first visit by a cardiologist, who also collected information on the medical history. Documented CV disease included history of angina pectoris, myocardial infarction, heart failure, coronary and/or carotid revascularization procedures, transitory ischemic attack, and stroke (Izzo et al., 2015b; Trimarco et al., 2023a). Arterial blood pressure was measured using auscultatory or oscillometric semiautomatic sphygmomanometers, attended by physicians were, with appropriate-size cuffs (Trimarco et al., 2023b). According to current guidelines on hypertension (Williams et al., 2018), we measured systolic and diastolic BP after 5 min resting in the sitting position, 3 times at 1 minute interval. Office follow-up visits were scheduled with a ~6-month interval. Lipid profile and fasting glucose were evaluated via standard methods (Pansini et al., 2022; Mone et al., 2023c). Diabetes was defined as history of diabetes, presence of fasting blood glucose ≥126 mg/dl confirmed on at least two different occasions, or use of any anti-diabetic medication(s) (Mone et al., 2022; Mone et al., 2023a; Mone et al., 2023b; Trimarco et al., 2023b). We estimated the glomerular filtration rate applying the “Chronic Kidney Disease Epidemiology Collaboration” (CKD-EPI) equation (Mancusi et al., 2018; Trimarco et al., 2023a).
Echocardiography

Transthoracic echocardiographic examinations were performed using phased-array devices following a standardized protocol (Lembo et al., 2022). Echocardiograms were digitally remastered and read off-line by an expert reader with the supervision of a senior faculty member, on a dedicated workstation. LVH was established by prognostically validated sex-specific cut-off values for LV mass/height: >50 g/m$^{2.7}$ in men and >47 g/m$^{2.7}$ in women (de Simone et al., 2018; Lembo et al., 2020a). Relative wall thickness was assessed as the ratio of posterior wall thickness and end-diastolic LV internal radius and was considered augmented for values ≥0.43 for either sex (de Simone et al., 2018; Cameli et al., 2020). LV ejection fraction was quantified using the Simpson biplane method in orthogonal apical chamber views (Galderisi et al., 2017; Lembo et al., 2020b; Gambardella et al., 2022).

Outcomes

The primary endpoint was a composite of nonfatal or fatal myocardial infarction, nonfatal or fatal stroke, heart failure requiring hospitalization, de novo angina, sudden cardiac death, myocardial revascularization, and carotid stenting. Secondary endpoint was a composite of primary endpoints plus ischemic attack and atrial fibrillation. The rate of CV events related to primary and secondary endpoints developed during the follow-up was evaluated to the first occurrence. Long term CV events were registered by direct contact with patients’ general practitioners or in clinical follow-up visits.

Statistical analysis

We used IBM SPSS 23 (IBM Corporation, Armonk, NY, USA) to perform statistical analyses. Regarding descriptive statistics, continuous variables are presented as mean ± SD or as median and interquartile range (IQR) depending on their distribution, whilst categorical variables are presented
as percentages. The endpoints were examined via adjusted Cox proportional hazards analyses calculating the incidence of primary and secondary endpoints in each group. The average achieved BP values up to the occurrence of the primary event or throughout the follow-up period when no endpoint of interest was regarded as the values characterizing the entire treatment period. The hazard ratio was adjusted for baseline covariates, including age, sex, SBP, DBP, heart rate, BMI, fasting glycemia, smoking status, and CKD-EPI in order to reduce the influence of potential confounders. Two sided $P<0.05$ was recognized statistically significant.

**Results**

We analyzed data from 9511 hypertensive patients (43% females), mean age 56.7±12.8 years, 9.3% diabetics, with a median follow-up period of 33.6 [IQR 7.9-72.7] months.

Our population was divided in six groups (**Figure 1, Table 1**) according to the average achieved SBP levels and absence or presence of Echo-LVH: 1) ≤130 mmHg and no Echo-LVH (n=2069); 2)≤130 mmHg and Echo-LVH (n=802); 3) 130 to 139 mmHg and no Echo-LVH (n=1902); 4) 130 to 139 mmHg and Echo-LVH (n=986); 5) ≥140 mmHg and no Echo-LVH (n=1946); 6) ≥140 mmHg and Echo-LVH (n=1806).

Baseline characteristics of the study population divided according to the presence or absence of Echo-LVH and average achieved in-treatment SBP values are summarized in **Table 1**. Patients with Echo-LVH and any degree of SBP were older, had a higher prevalence of diabetes, lower values of CKD-EPI, and higher BMI than those without Echo-LVH. Within the group with LVH, patients with SBP ≥140 mmHg were the oldest and the ones presenting the highest impairment in CKD-EPI, fasting glycaemia, and prevalence of diabetes. The percentage of female patients was higher among patients with Echo-LVH. Smoke habit was less frequent in patients with Echo-LVH and SBP ≥ 140 mmHg. SBP and DBP at baseline were higher in patients with higher SBP at follow-up both in absence or presence of Echo-LVH, but patients with Echo-LVH exhibited higher values of baseline SBP when compared to patients without Echo-LVH who achieved the same average in-treatment
SBP values. As expected, LV mass index was higher in the group with Echo-LVH than in patients without LVH, and within the group with LVH it progressively increased according to SBP values. Similarly, LV relative wall thickness resulted higher in patients with LVH and in patients with higher SBP values. LV ejection fraction was lower in patients with LVH than in those without.

**Average Achieved BPs in the Study Groups**

During the follow-up, average achieved SBP and DBP values were generally comparable between the corresponding groups (*i.e.* with and without Echo-LVH), although SBP was slightly higher in the group with Echo-LVH than in the group without LVH among patients remaining at values ≥140 mmHg (Figure 2).

Patients with Echo-LVH displayed lower values of CKD-EPI than those without Echo-LVH, reaching the highest impairment in those with Echo-LVH and SBP ≥140 mmHg. Patients with Echo-LVH were treated with a higher number of drugs than those without Echo-LVH; specifically, patients with Echo-LVH and SBP ≥140 mmHg were the ones assuming the highest number of antihypertensive drugs. All types of medications were more frequently given to patients with Echo-LVH (Table 2).

**Rates of Endpoints**

The rates of primary and secondary endpoints recorded in the six groups obtained dividing our population according to the achieved SBP during the follow-up and the absence or presence of Echo-LVH are shown in Table 3. We found that patients with SBP >130 mmHg and Echo-LVH had a significantly higher rate of both primary and secondary endpoints than all other groups. Furthermore, we calculated the rates of primary and secondary endpoints when the study population was divided according to the achieved DBP (≤80 mmHg, 80-89 mmHg, ≥90 mmHg) and absence or presence of Echo-LVH. When the primary endpoint was considered, we found that the rate of CV events was higher in the groups of patients with Echo-LVH and DBP ≤80 mmHg as compared to
those with comparable DBP levels but without Echo-LVH (Table 3). When considering secondary endpoints, the highest rate of events was reached in the group with DBP ≤80 mmHg and Echo-LVH.

With a total of 162 primary (1.7%) and 398 secondary (4.2%) events, the present study population does not allow a separate analysis for each single component of the composite endpoint due to limited statistical power.

By a Cox multivariable regression analysis, after adjusting for sex, age, average DBP, baseline heart rate, BMI, fasting glycaemia, CKD-EPI, and smoking habit, the primary endpoint was independently associated with SBP ≥140 mmHg and Echo-LVH (Figure 3, Table 4A). Similarly, by applying a Cox multivariable model (Table 4B), after adjusting for the same confounders, the composite of the secondary endpoint was again independently associated with Echo-LVH and SBP ≥140 mmHg.

Discussion

This study was planned to define BP targets in hypertensive patients with Echo-LVH, since international guidelines for the management of arterial hypertension suggest to reduce BP below 130/80 mmHg but a couple of reports (Okin et al., 2012; Heimark et al., 2023) have described an excess mortality in patients with ECG-LVH and in-treatment BP<130/80 mmHg. To shed light on this important aspect, we studied a large population of patients with hypertension but without a history of CV events within our “Campania Salute Network” registry. Contrary to the two previous cited studies, in the present one Echo-LVH was used instead of ECG-LVH. Patients were divided in groups according to the presence or absence of Echo-LVH and the average SBP and DBP achieved during a long-term follow-up (Figure 1) and the rates of non-fatal and fatal CV events were compared. While failing to demonstrate any further benefit in CV prognosis by reducing SBP below 130 mmHg in absence of Echo-LVH, our results indicate that in patients with hypertension and Echo-LVH the reduction of SBP ≤130 mmHg is associated with significantly attenuated rates of CV
events, which were no longer different from those of patients without Echo-LVH. In contrast, when we divided our population on the basis of DBP values and absence or presence of Echo-LVH, we found that patients with LVH and achieved in treatment DBP <90 mmHg had a higher rate of both primary and secondary endpoints when compared to the corresponding DBP groups without echo-LVH.

Average achieved SBP and DBP values were strictly comparable between corresponding groups with and without Echo-LVH, thus supporting that in our study differences in CV outcomes not depended on differences in BP values but on differences in LVH, as previously suggested (Heimark et al., 2023). Furthermore, the results of the Cox multivariate regression analysis adjusting for age, sex, mean DBP, baseline heart rate, BMI, CKD-EPI and smoking habit, confirm that the combination of Echo-LVH and SBP≥140 mmHg is the main determinant of primary and secondary endpoint in our population; yet, a reduction of average SBP ≤130 mmHg is able to significantly improve CV prognosis of patients with Echo-LVH so that their rate of CV events is no longer different from the one of patients without Echo-LVH.

Interestingly, our findings are in line with those of the SPRINT trial (McEvoy et al., 2016), showing that reducing SBP below 130 mmHg in high risk patients with hypertension, such as those with Echo-LVH, is accompanied by a further reduction in the rate of CV events when compared to patients with Echo-LVH who achieved average SBP values comprised between 130 and 139 mmHg.

Remarkably, our results indicate that the data by Heimark and coworkers (Heimark et al., 2023) showing no reduction of the primary endpoint on account of an augmented risk of cardiac and all causes mortality in individuals with ECG-LVH cannot be extrapolated and extended to patients with Echo-LVH. Indeed, it should be underlined that the two populations are rather different, since in our study, in contrast with the one by Heimark et al. (Heimark et al., 2023), we excluded patients with prevalent CV disease, thereby resulting in a lower rate of CV events, which prevented the possibility of a detailed powered analysis for each type of CV events. In addition, we used a
composite CV endpoint which was comprehensive of major and minor CV events as secondary endpoint.

Moreover, the precise correlation between Echo-LVH and ECG-LVH is quite debated and major discrepancies have been noted (Bacharova, 2009; Cheng et al., 2010; Narayanan et al., 2014): a recent report has demonstrated that actually there is a weak linear correlation between LV mass index and ECG-LVH and that ECG-LVH has a poor discriminative ability to detect Echo-LVH (Lv et al., 2021). Specifically, ECG-LVH criteria have been demonstrated to have low sensitivity and a low positive predictive value (Lv et al., 2021). Hence, ultrasound and ECG assessments might convey distinctive risk information in hypertensive patients, reflecting for instance anatomic vs. electrical remodeling, respectively.

The evaluation of both hard and soft endpoints in our study corroborated results that had been previously obtained analyzing hard endpoints in patients with a high-risk profile, extending these findings to a larger number of CV complications, such as atrial fibrillation, that could have an impact on the health system. Thus, our data highlight that too low DBP values achieved during the anti-hypertensive treatment in patients with hypertension but with SBP at target, represent a predictor of CV complications in a manner independent of relevant confounders, such as CV risk factors, SBP at follow-up, renal function and, most importantly, target organ damage. Unfortunately, since our analysis merged a large number of possible CV complications, the potential mechanism underlying the negative effects of too low DBP values are hardly determined. Nonetheless, one mechanism could be represented by the low diastolic perfusion of the coronary circulation, as revealed by an analysis performed within the population of the ARIC (“Atherosclerosis Risk in Communities”), showing a linear inverse relation linking high-sensitivity cardiac troponin-T and DBP when DBP was <65mmHg and SBP was >120mmHg, indicating a subclinical injury of the myocardium (McEvoy et al., 2016). This phenomenon could be even exacerbated in patients with hypertension and with LVH in whom coronary perfusion is already impaired because of coronary rarefaction (Mohammed et al., 2015; Lembo et al., 2023). Thus, our
results indicate that therapeutic strategies in patients with Echo-LVH should aim at reducing SBP≤130mmHg being careful to not reduce DBP≤80mmHg.

On the basis of the observation that patients with ECG-LVH achieving an average SBP below 130 mmHg exhibit an augmented mortality (both all-cause and cardiac) without any reduction in CV events, and the consideration that a correlation linking LVH by echocardiography and ECG exists, it has been suggested caution must be used in managing middle-aged and older patients with hypertension with LVH determined by both ECG and Echo to SBP targets below 130 mmHg, at least until further clinical information will be available regarding the exact BP targets to be reached in hypertensive patients with LVH assessed by echocardiography. In contrast, our data demonstrate that reducing the in-treatment average SBP below 130 mmHg may be useful in hypertensive patients with Echo-LVH, but particular attention should be paid to DBP in order to reduce the occurrence of disorders like atrial fibrillation and transient ischemic attacks. These analyses are observational, and we are not able to give strict indications about the levels of SBP and DBP which are considered to be safe, nor to determine where exactly the risks start to overcome the benefits of aggressively reducing SBP. For these purposes, adequately powered trials aimed at specifically assessing this primary goal should be performed.

**Authorship contributions**

Participated in research design: V.T., G.S., and B.T.


Performed data analysis: M.L. and R.I.

Wrote or contributed to the writing of the manuscript: M.L., V.T., R.I., G.S., and B.T.
Footnotes

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Financial disclosure statement

No author has an actual or perceived conflict of interest with the contents of this article.

Data availability statement

Reasonable requests to access the data used in these analyses can be made to the first Authors.
References


characteristics of true and apparent treatment resistant hypertension in the Campania Salute Network. *Int J Cardiol* **184**:417-419.


Figure Legends

**Figure 1.** Cartoon depicting the main characteristics of the six study groups.

**Figure 2.** Diagram showing comparable values at different ranges of achieved in-treatment SBP (≤130 mmHg, 130-139 mmHg, ≥140 mmHg) *(panel A)* and DBP (≤80 mmHg, 80-89 mmHg, ≥90 mmHg) *(panel B)* during the follow-up in patients with and without LVH.

DBP: diastolic blood pressure, LVH: left ventricular hypertrophy, SBP: systolic blood pressure.

**Figure 3.** Risk of the primary endpoint in the study population divided according to SBP values (≤130 mmHg, 130-139 mmHg, ≥140 mmHg) and presence or absence of Echo-LVH.
Table 1. Baseline characteristics of the study population divided according to the presence of LVH and systolic blood pressure values. CKD = chronic kidney disease, DBP = diastolic blood pressure, LVH = left ventricular hypertrophy, SBP = systolic blood pressure. *: p<0.05 group 1 vs 4; §: p<0.05 group 2 vs 5; ^: p<0.05 group 3 vs 6.

<table>
<thead>
<tr>
<th></th>
<th>No LVH &amp; SBP ≤130 mmHg (n=2069) (group 1)</th>
<th>No LVH &amp; 130&lt;SBP≤139 mmHg (n=1902) (group 2)</th>
<th>No LVH &amp; SBP ≥140 mmHg (n=1946) (group 3)</th>
<th>LVH &amp; SBP ≤130 mmHg (n=802) (group 4)</th>
<th>LVH &amp; SBP 130&lt;SBP≤139 mmHg (n=986) (group 5)</th>
<th>LVH &amp; SBP ≥140 mmHg (n=1806) (group 6)</th>
<th>Overall p value</th>
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<tr>
<td>Age (years)</td>
<td>49.4±11.1</td>
<td>49.5±11.4</td>
<td>50.5±13.0</td>
<td>55.5±11.0*</td>
<td>56.5±10.6§</td>
<td>58.5±11.3^</td>
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<td>SBP (mmHg)</td>
<td>128.3±12.5</td>
<td>139.7±12.2</td>
<td>152.8±15.6</td>
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<td>142.0±13.7§</td>
<td>157.9±19.7^</td>
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<td>DBP (mmHg)</td>
<td>84.3±10.1</td>
<td>89.2±9.4</td>
<td>92.7±10.7</td>
<td>89.1±10.5</td>
<td>92.4±11.3§</td>
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<td>Heart rate (bpm)</td>
<td>70.2±21.5</td>
<td>71.0±21.5</td>
<td>72.6±11.9</td>
<td>69.1±21.8</td>
<td>70.4±11.3§</td>
<td>71.3±21.4^</td>
<td>&lt;0.0001</td>
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<tr>
<td>Total cholesterol (mg/dl)</td>
<td>203.5±37.9</td>
<td>204.6±39.1</td>
<td>205.1±40.3</td>
<td>206.0±40.5</td>
<td>206.4±38.9</td>
<td>204.1±39.7</td>
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<td>Fasting glycaemia (mg/dl)</td>
<td>94.8±17.4</td>
<td>95.3±19.4</td>
<td>97.6±21.6</td>
<td>99.2±21.1*</td>
<td>101.8±25.5§</td>
<td>104.7±29.3^</td>
<td>&lt;0.0001</td>
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<td>CKD-EPI</td>
<td>83.8±15.4</td>
<td>83.6±15.4</td>
<td>83.4±16.4</td>
<td>78.8±16.3*</td>
<td>78.4±15.1§</td>
<td>75.8±17.4^</td>
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<td>HDL-cholesterol (mg/dl)</td>
<td>50.8±12.5</td>
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<td>50.5±12.6</td>
<td>49.7±13.1</td>
<td>49.8±13.1</td>
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<tr>
<td>Female sex (%)</td>
<td>806 (39.0)</td>
<td>717 (37.7)</td>
<td>812 (41.7)</td>
<td>379 (47.3)*</td>
<td>75 (48.2)§</td>
<td>926 (51.3)^</td>
<td>&lt;0.0001</td>
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<td>Smoking habit (%)</td>
<td>436 (21.1)</td>
<td>370 (19.5)</td>
<td>349 (17.9)</td>
<td>148 (18.5)</td>
<td>180 (18.3)</td>
<td>226 (12.5)^</td>
<td>&lt;0.0001</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>26.7±3.7</td>
<td>26.7±3.5</td>
<td>26.9±3.9</td>
<td>29.5±4.5*</td>
<td>29.3±4.5§</td>
<td>29.6±4.6^</td>
<td>&lt;0.0001</td>
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<tr>
<td>Diabetes (%)</td>
<td>115 (5.6)</td>
<td>102 (5.4)</td>
<td>146 (7.5)</td>
<td>77 (9.6)*</td>
<td>126 (12.8)§</td>
<td>315 (17.4)^</td>
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<td>LV mass index (g/m²)</td>
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<td>41.4±4.9</td>
<td>42.9±4.8</td>
<td>54.7±6.2*</td>
<td>55.7±7.1§</td>
<td>57.3±8.4^</td>
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<tr>
<td>LV Relative wall thickness</td>
<td>0.37±0.02</td>
<td>0.37±0.03</td>
<td>0.38±0.03</td>
<td>0.38±0.04*</td>
<td>0.39±0.04§</td>
<td>0.40±0.04^</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>66.8±3.6</td>
<td>66.7±3.5</td>
<td>66.7±3.8</td>
<td>64.9±5.2*</td>
<td>65.1±4.3§</td>
<td>64.8±4.3^</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>No LVH &amp; SBP ≤130 mmHg (n=2069) (group 1)</td>
<td>No LVH &amp; 130&lt;SBP≤139 mmHg (n=1902) (group 2)</td>
<td>No LVH &amp; SBP ≥140 mmHg (n=1946) (group 3)</td>
<td>LVH &amp; SBP ≤130 mmHg (n=802) (group 4)</td>
<td>LVH &amp; 130&lt;SBP≤139 mmHg (n=986) (group 5)</td>
<td>LVH &amp; SBP ≥140 mmHg (n=1806) (group 6)</td>
<td>Overall p value</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------------------</td>
<td>---------------------------------------------</td>
<td>------------------------------------------</td>
<td>---------------------------------------</td>
<td>----------------------------------------</td>
<td>-----------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>CKD-EPI at the end of the follow-up</td>
<td>81.7±15.3</td>
<td>81.1±15.4</td>
<td>80.6±17.0</td>
<td>76.8±16.4*</td>
<td>75.0±16.1§</td>
<td>72.8±18.4^</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Drugs in at least 50% of control visits</td>
<td>1.3±1.0</td>
<td>1.4±1.0</td>
<td>1.5±1.1</td>
<td>1.7±1.0*</td>
<td>1.8±1.0§</td>
<td>2.0±1.1^</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renin-angiotensin system drugs inhibitors (%)</td>
<td>1481 (71.6)</td>
<td>1401 (73.7)</td>
<td>1373 (70.6)</td>
<td>663 (82.7)*</td>
<td>826 (83.8)§</td>
<td>1502 (83.2)^</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dihydropyridine calcium channel blockers (%)</td>
<td>328 (15.9)</td>
<td>363 (19.1)</td>
<td>485 (24.9)</td>
<td>206 (25.7)*</td>
<td>275 (27.9)§</td>
<td>710 (39.3)^</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>685 (33.1)</td>
<td>674 (35.4)</td>
<td>705 (36.2)</td>
<td>368 (45.9)*</td>
<td>490 (49.7)§</td>
<td>965 (53.5)^</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>473 (22.9)</td>
<td>435 (22.9)</td>
<td>521 (26.8)</td>
<td>193 (24.1)</td>
<td>252 (25.6)</td>
<td>561 (31.1)^</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antiplatelet therapy (%)</td>
<td>230 (11.6)</td>
<td>196 (10.6)</td>
<td>233 (12.6)</td>
<td>164 (21.4)*</td>
<td>204 (21.3)§</td>
<td>395 (23.1)^</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>301 (15.1)</td>
<td>265 (14.4)</td>
<td>241 (13.0)</td>
<td>142 (18.5)*</td>
<td>195 (20.3)§</td>
<td>317 (18.6)^</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Table 2.** Characteristics of the study population during the follow-up divided according to the presence of LVH and systolic blood pressure values.

Abbreviations as in Table 1.
### Table 3

Primary and secondary endpoints in the study population divided according to the presence of LVH and systolic (Panel A) and diastolic (Panel B) blood pressure values.

#### Panel A

<table>
<thead>
<tr>
<th></th>
<th>No LVH &amp; SBP ≤130 mmHg (n=2069) (group 1)</th>
<th>No LVH &amp; SBP &gt;130 &amp; ≤139 mmHg (n=1902) (group 2)</th>
<th>No LVH &amp; SBP ≥140 mmHg (n=1946) (group 3)</th>
<th>LVH &amp; SBP ≤130 mmHg (n=802) (group 4)</th>
<th>LVH &amp; SBP &gt;130 &amp; ≤139 mmHg (n=986) (group 5)</th>
<th>LVH &amp; SBP ≥140 mmHg (n=1806) (group 6)</th>
<th>Overall p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint (%)</td>
<td>21 (1.0)</td>
<td>19 (1.0)</td>
<td>39 (2.0)</td>
<td>9 (1.1)</td>
<td>22 (2.2)§</td>
<td>52 (2.9)^</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Secondary endpoint (%)</td>
<td>65 (3.1)</td>
<td>51 (2.7)</td>
<td>65 (3.3)</td>
<td>32 (4.0)</td>
<td>61 (6.2)§</td>
<td>124 (6.9)^</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

#### Panel B

<table>
<thead>
<tr>
<th></th>
<th>No LVH &amp; DBP ≤80 mmHg (n=1573) (group 1)</th>
<th>No LVH &amp; DBP &gt;80 &amp; ≤89 mmHg (n=2865) (group 2)</th>
<th>No LVH &amp; DBP ≥90 mmHg (n=1446) (group 3)</th>
<th>LVH &amp; DBP ≤80 mmHg (n=1019) (group 4)</th>
<th>LVH &amp; DBP &gt;80 &amp; ≤89 mmHg (n=1644) (group 5)</th>
<th>LVH &amp; DBP ≥90 mmHg (n=964) (group 6)</th>
<th>Overall p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint (%)</td>
<td>24 (1.5)</td>
<td>35 (1.2)</td>
<td>20 (1.3)</td>
<td>28 (2.7)*</td>
<td>36 (2.2)§</td>
<td>19 (2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary endpoint (%)</td>
<td>65 (4.1)</td>
<td>87 (3.0)</td>
<td>29 (2.0)</td>
<td>80 (7.8)*</td>
<td>95 (5.7)§</td>
<td>42 (4.4)^</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
### Panel A.

<table>
<thead>
<tr>
<th>Variable</th>
<th>aHR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Female vs Male)</td>
<td>0.45</td>
<td>0.31, 0.67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.02, 1.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVH &amp; SBP≥140 mmHg</td>
<td>2.19</td>
<td>1.19, 4.05</td>
<td>0.012</td>
</tr>
<tr>
<td>Average DBP during the follow-up</td>
<td>1.01</td>
<td>0.98, 1.04</td>
<td>0.513</td>
</tr>
<tr>
<td>Heart rate at baseline</td>
<td>1.00</td>
<td>0.99, 1.01</td>
<td>0.622</td>
</tr>
<tr>
<td>Fasting glycaemia at baseline</td>
<td>1.01</td>
<td>1.00, 1.01</td>
<td>0.031</td>
</tr>
<tr>
<td>CKD-EPI at baseline</td>
<td>0.99</td>
<td>0.98, 1.00</td>
<td>0.148</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>1.70</td>
<td>1.12, 2.55</td>
<td>0.011</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.97</td>
<td>0.93, 1.02</td>
<td>0.268</td>
</tr>
</tbody>
</table>

### Panel B.

<table>
<thead>
<tr>
<th>Variable</th>
<th>aHR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Female vs Male)</td>
<td>0.75</td>
<td>0.61, 0.93</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age</td>
<td>1.06</td>
<td>1.04, 1.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVH &amp; SBP≥140 mmHg</td>
<td>1.52</td>
<td>1.06, 2.20</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Average DBP during the follow-up</td>
<td>1.01</td>
<td>0.98, 1.02</td>
<td>0.580</td>
</tr>
<tr>
<td>Heart rate at baseline</td>
<td>1.00</td>
<td>0.99, 1.01</td>
<td>0.660</td>
</tr>
<tr>
<td>Fasting glycaemia at baseline</td>
<td>1.00</td>
<td>0.99, 1.01</td>
<td>0.257</td>
</tr>
<tr>
<td>CKD-EPI at baseline</td>
<td>1.00</td>
<td>0.99, 1.01</td>
<td>0.925</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>1.26</td>
<td>0.95, 1.66</td>
<td>0.106</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.00</td>
<td>0.97, 1.03</td>
<td>0.885</td>
</tr>
</tbody>
</table>

**Table 4.** Cox multiple regression model to test possible predictors of the primary (Panel A) and secondary endpoints (Panel B) in the hypertensive population.
Figure 1

No LVH

- SBP ≤130 mmHg
- Group 1

- 130<SBP≤139 mmHg
- Group 2

- SBP ≥140 mmHg
- Group 3

LVH

- SBP ≤130 mmHg
- Group 4

- 130<SBP≤139 mmHg
- Group 5

- SBP ≥140 mmHg
- Group 6
Figure 2

A. Average SBP

- ≥140 mmHg
- 130-139 mmHg
- ≤130 mmHg

B. Average DBP

- ≥90 mmHg
- 80-89 mmHg
- ≤80 mmHg
Figure 3

Hazard Risk of Primary Endpoint against FU (months)

- No LVH & SBP ≤ 130
- No LVH & 130 < SBP ≤ 139
- No LVH & SBP ≥ 140
- LVH & SBP ≤ 130
- LVH & 130 < SBP ≤ 139
- LVH & SBP ≥ 140