Target Organ Damage and Target Systolic Blood Pressure in Clinical Practice: The Campania Salute Network

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BACKGROUND

Lowering systolic blood pressure (SBP) below the conventional threshold (140 mm Hg) reduces left ventricular (LV) hypertrophy and incident cardiovascular (CV) events. We assessed whether different thresholds of SBP as the average value during follow-up (FU) have different impact on changes in target organ damage (TOD).

METHODS

From the Campania Salute Network registry, we selected 4,148 hypertensive patients with average SBP-FU <140 mm Hg, and without history of prevalent CV or chronic kidney disease (i.e., <stage IV CKD). Patients were divided in “Tight” (SBP-FU <130 mm Hg) or “Usual” (SBP-FU ≥130) BP control. At baseline and at the last available control visit, we assessed LV mass index (LVMi, g/m²), carotid intimal-medial thickness (IMT, mm), and glomerular filtration rate by CKD-EPI equation (GFR, ml/min/1.73 m²) as markers of TOD. Time trend of TOD for tight and usual subgroups were compared, adjusting for significant confounders.

RESULTS

During a median of 74 months (interquartile range: 35–108 months), 1,824 patients (44%) were classified as tight control. They were younger, with less prevalent obesity, diabetes, lower initial LVMi, and IMT, and were taking less Ca++-channel blockers during FU than the usual control subgroup (all P < 0.05). In both subgroups, there were no changes over time in LVMi and GFR, whereas the IMT increased during the FU (P < 0.004), with no significant effect of degree of SBP control.

CONCLUSIONS

In a registry of treated hypertensive patients from a tertiary care center, progression of TODs is not related to average SBP during FU.

Keywords: blood pressure; carotid atherosclerosis; carotid plaque; carotid ultrasound; echocardiography; hypertension; left ventricular hypertrophy; renal function.

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Target Organ Damage (TOD) in hypertension is a cardinal manifestation of preclinical cardiovascular (CV) disease that strongly predicts major adverse CV end-points. 3, 4, 10–12

Thus, prevention of CV events has been linked to the ability of antihypertensive treatment to reduce TOD, a proxy of decreased CV risk, as demonstrated in clinical trials. 3–7

Among markers of TOD, LVH is the most widely studied in trials, cohorts and observational studies, and reduction of electrocardiographic or echocardiographic LVH is associated with substantial reduction of CV events. 6, 8

Aggressive SBP control and attention to metabolic aspects are critical to promote regression of LVH. 7 Furthermore early initiation of antihypertensive treatment is an important issue to control the progression of atherosclerosis. 5 While the optimal target SBP for minimizing CV risk is largely debated, 2, 10–12 there is little information on whether different targets of SBP are associated with different evolution of TOD. 6, 13 in a real-world context.

Accordingly, we analyzed whether a lower achieved threshold of SBP during follow-up (FU) is associated with more favorable evolution of TOD, in a large registry of hypertensive patients.

METHODS

Study population

The Campania Salute Network (CSN) Registry (ClinicalTrials.gov Identifier: NCT02211365) is an open registry of treated hypertensive patients, coordinated by the Hypertension Research Center of the Federico II University Hospital and networked with general practitioners and community hospitals in the Campania region in Southern Italy. Signed informed consent was obtained from all participants.
The local Ethics Committee approved the database generation. Detailed characteristics of this population and procedures of the CSN have been previously reported. Patients referred to the Hypertension Research Center undergo a work-up including lab tests and ultrasound and their therapy was adjusted, when needed.

Main inclusion criterion for the present analysis was office systolic blood pressure (SBP) <140 mm Hg, as the average value from all available control visits during FU for each patient. Other inclusion criteria were: age >18, no history of CV disease (myocardial infarction, coronary revascularization, stroke, congestive heart failure, or TIA) or atrial fibrillation, ejection fraction >50%, no prevalent chronic kidney disease (CKD) more than stage III (GFR by CKD-EPI equation ≥30 ml/min/1.73 m²), and at least 1 year FU with available echocardiograms and carotid ultrasound.

Thus, the final study population consisted of 4,148 treated hypertensive patients. Selection process of the study population is reported in Figure 1.

Measurements and definitions

Diabetes was defined according to 2007 ADA criteria (fasting plasma glucose >125 mg/dl or antidiabetic treatment). Obesity was defined as a BMI ≥30 kg/m².

At each visit in the outpatient clinic, SBP, and diastolic BP were measured by expert physicians with standard aneroid sphygmomanometer after 5 minutes resting in sitting position, according to current guidelines. BP was measured 3 times at 2-minute intervals and the average of the last 2 BP was taken as the office BP. The average SBP and diastolic BP during FU was obtained for each patient, as previously reported.

Echocardiography

All echocardiograms were recorded by commercial machines using a standardized protocol. Echocardiograms were read off line by one expert reader under the supervision of a senior faculty member, on dedicated workstations (MediMatic, Genoa, Italy).

Measurements were made according to the ASE/EAE recommendations. LVM was estimated by a necropsy-validated formula and normalized for height in meters to the power of 2.7 (LV mass index, LVMi). LVH was defined as LVMi ≥50 g/m² in men and ≥47 g/m² in women. Relative wall thickness, as posterior wall thickness divided by LV internal radius, was used as a measure of LV concentricity. LV concentric geometry was defined as a relative wall thickness ≥0.43 for both genders. LV volumes were calculated by the z-derived method, and used to calculate ejection fraction.

Carotid ultrasound

Carotid ultrasound was performed on patients in the supine position, with the neck extended in mild rotation. Examinations were recorded on S-VHS videotapes and analyzed as previously reported. The maximal arterial IMT was estimated offline in up to 12 arterial walls, including the right and the left, near and far distal common carotid (1 cm),

Figure 1. Study population selection process. Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; EF, ejection fraction; SBP, systolic blood pressure.
bifurcation, and proximal internal carotid artery, using an image-processing dedicated workstation (MediMatic). Evidence of IMT value higher than 1.5 mm was considered as "plaque."  

**Statistical analysis**

Data were analyzed by IBM-SPSS 23.0 (IBM Corporation, Armonk, NY). Data are presented as mean ± 1 SD, or median and interquartile range for skewed variables, and as percentages for categorical variables. 

Classification in “Tight” or “Usual” BP control was done on the basis of the average value of all SBP measurements taken in the outpatient clinic during FU, as:

\[ \sum_{n}^{2} SBP - FU + n \]

where “SBP–FU” is SBP measured during FU and “n” is the number of control visits after the initial admission to the registry. Patients with tight BP control exhibited the average SBP-FU < 130 mm Hg, whereas those with usual BP control had the average SBP-FU ≥ 130.

To compare the effect of the different levels of achieved BP, a linear mixed model was run, using restrictive maximum likelihood method, baseline and final outpatients control as the repeated variable, and the TOD marker as the dependent variable. Interaction among repeated variable, type of BP control, and covariates were also tested. Estimated marginal means and 95% confidence intervals are reported for TOD.

As previously reported, single classes of medications, including anti-renin–angiotensin system drugs (i.e., ACE inhibitors and/or AT1 receptor antagonists), Ca++ channel blockers, β-blockers, and thiazide diuretics, were considered as covariate in the multivariate analysis if used in more than 50% of control visits during the follow-up period. Changes in LVMi, IMT, and GFR and rate of annual change have also been analyzed. The null hypothesis was rejected at a 2-tailed P value of ≤ 0.05.

**RESULTS**

The study population consisted of 4,148 treated hypertensive patients, (age 52 ± 10 years, 41% women, 23% obese, 8% diabetic). We classified 1,824 patients (44%) as the “Tight” control group and 2,324 patients as the “Usual” control group.

Table 1 displays the baseline characteristics of usual and tight control groups. Patients with usual SBP control were older, more frequently obese, diabetic with longer duration of hypertension, higher initial SBP and diastolic BP, heart rate and had longer duration of FU than patients with tight SBP control (all P < 0.05).

Table 2 shows that initial LVMi, relative wall thickness, and IMT were higher in the usual than in the tight control. Initial prevalence of LVH and carotid plaque were also more frequent in the usual than in the tight control (all P < 0.01).

Table 3 compares distribution of antihypertensive therapy during FU. Patients with usual control received more

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**Table 1. Baseline characteristic of patients with tight or usual SBP control**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Tight control (N = 1,824)</th>
<th>Usual control (N = 2,324)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average follow-up SBP &lt; 130 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.3 ± 10.3</td>
<td>52.2 ± 10.9</td>
<td>0.007</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>40.5</td>
<td>41</td>
<td>0.52</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.3 ± 3.9</td>
<td>27.5 ± 4</td>
<td>0.03</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>20.3</td>
<td>24.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>6.6</td>
<td>8.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>95.9 ± 18.7</td>
<td>97.8 ± 22.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>204.9 ± 38.3</td>
<td>206 ± 38.4</td>
<td>0.34</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>50.8 ± 12.5</td>
<td>50.5 ± 13</td>
<td>0.53</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>130.9 ± 72.3</td>
<td>135.5 ± 78</td>
<td>0.05</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>82.2 ± 14.8</td>
<td>81.7 ± 14.8</td>
<td>0.26</td>
</tr>
<tr>
<td>Duration of hypertension (years)</td>
<td>4.9 ± 5.8</td>
<td>5.6 ± 6.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Initial SBP (mm Hg)</td>
<td>129.8 ± 13.1</td>
<td>140.6 ± 13.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Initial DBP (mm Hg)</td>
<td>85.2 ± 10.2</td>
<td>89.1 ± 9.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Baseline HR (bpm)</td>
<td>72.9 ± 10.7</td>
<td>74.6 ± 11.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Average follow-up SBP (mm Hg)</td>
<td>123.9 ± 4.6</td>
<td>134.6 ± 2.9</td>
<td></td>
</tr>
<tr>
<td>Average follow-up DBP (mm Hg)</td>
<td>79.9 ± 5.1</td>
<td>84 ± 5.3</td>
<td></td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>6 ± 4.2</td>
<td>6.4 ± 4.3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Abbreviations: DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate; SBP, systolic blood pressure.
Table 2. Target organ damage of patients with tight or usual SBP control

<table>
<thead>
<tr>
<th>Variables</th>
<th>Tight control Average follow-up SBP &lt; 130 mm Hg (N = 1,824)</th>
<th>Usual control Average follow-up SBP ≥ 130 &lt; 140 mm Hg (N = 2,324)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial LV mass (g/m²)</td>
<td>44.6 ± 7.8</td>
<td>46.3 ± 8.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Initial relative wall thickness</td>
<td>0.37 ± 0.3</td>
<td>0.38 ± 0.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Initial carotid IMT (mm)</td>
<td>1.4 ± 0.6</td>
<td>1.5 ± 0.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Baseline LV hypertrophy (%)</td>
<td>26.9</td>
<td>33.8</td>
<td></td>
</tr>
<tr>
<td>Baseline carotid plaque (%)</td>
<td>37.4</td>
<td>42.3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Abbreviations: CV, cardiovascular; IMT, intimal media thickness; LV, left ventricular; SBP, systolic blood pressure.

Table 3. Frequency of antihypertensive meds during FU in patients on tight and usual BP control

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tight control Average follow-up SBP &lt; 130 mm Hg (N = 1,824)</th>
<th>Usual control Average follow-up SBP ≥ 130 &lt; 140 mm Hg (N = 2,324)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-RAS (%)</td>
<td>81.7</td>
<td>81.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Ca²⁺channel blockers (%)</td>
<td>18</td>
<td>21.6</td>
<td>0.005</td>
</tr>
<tr>
<td>B-blockers (%)</td>
<td>23.7</td>
<td>24.7</td>
<td>0.48</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>38.7</td>
<td>41</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; FU, follow-up; RAS, renin–angiotensin system; SBP, systolic blood pressure.

prescription of Ca-channel-blockers than the tight control group (P = 0.005), whereas no other significant differences were found in the other medications.

Table 4 shows comparison between baseline and final values of the 3 markers of TOD in the groups with tight or usual BP control, adjusted for age, baseline office SBP, sex, duration of FU, diabetes, obesity, and therapy with Ca²⁺-channel blockers. After a median FU of 74 months (interquartile range 35–108 months), there was no significant change in LVMi. Also, the slight decrease in GFR in both groups was not statistically significant and no difference between tight and usual SBP control groups could be detected. In contrast, IMT increased during FU in either groups (P < 0.005), without significant difference related to SBP control during FU (Table 4). Figure 2 shows the percent variation for each TOD after adjusting for covariates.

DISCUSSION

Our study demonstrates that in a tertiary care center registry of treated hypertensive patients without prevalent CV disease and with normal ejection fraction, TOD (LVMi, IMT, and GFR) does not decrease over time in relation of tightness of SBP control. Rather, in contrast to what might be expected:

i) LVMi does not change over time, GFR tends to deteriorate and vascular signs of TOD significantly worsen, independently of target BP;

ii) Progression of TOD is scarcely influenced by type of antihypertensive medications.

While current European guidelines recommend a SBP <140 mm Hg,3 there are trials suggesting lower thresholds, which are now translated into the new American Guidelines.12 The Studio Italiano Sugli Effetti CARDIO vasculari del Controllo della Pressione Arteriosa SIStolica (Cardio-Sis) and a subanalysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) suggested that a SBP <130 mm Hg and <120 mm Hg, respectively, is more effective in reducing prevalence of ECG LVH.5,13 Most recently, the Systolic Blood Pressure Intervention Trial (SPRINT) reported reduced CV events in hypertensive patients with SBP target <120 mm Hg, but a higher rate of GFR decline than in patients with SBP target <140 mm Hg.11 The new Intersociety American guidelines also reduced the threshold for definition of hypertension to 130/80 mm Hg.12

Based on the assumption that effects of antihypertensive therapy on TOD is a surrogate of CV end-points,26 we evaluated whether target BP achieved during FU may influence the ability to control progression, regression, or reduction of TOD in a real-world context of relatively unselected hypertensive patients without prevalent CV disease and under antihypertensive therapy. The result of the analysis was unexpected, though in line with previous analysis in the CSN as well as in population-based studies.7,27

The CSN gathers almost all hypertensive patients primarily referred to general practitioners (GPs) or Community Hospitals in the network, minimizing selection bias. However, in contrast with participants included in many clinical trials who often exhibit short duration of hypertension and are untreated, the CSN patients have a long-lasting history of hypertension and come to our outpatient clinic, after variable periods and cycles of antihypertensive treatment. In addition, in general, at the time of the first visit in the Hypertension Research Center, about 30% of referred patients are already in good BP control, according to current guidelines. Thus, it is possible that the effect achievable with antihypertensive treatment had already been obtained in many patients, and the changes in TOD could not be expected to be substantial,
when starting observation from the first visit in our outpatient clinic. We cannot determine how many patients could have had their LVMI significantly reduced before their first contact with our Hypertension Center.

In the context of CSN, which represents the real clinical practice of antihypertension clinics, TOD reflects consolidated organ damage, possibly resistant to previous therapy, though often not effective for optimal BP reduction. Thus, the fact that LVH regression demonstrated in placebo-controlled, randomized, clinical trials, and several meta-analyses could not be confirmed in our analysis, even when control of BP was tight, could be expected. The selection imposed in clinical trials and meta-analyses remains an important problem when transferred to the real world context of patients with history, characteristics and risk profile that do not reflect the trial selection. In addition, the lack of LVH regression despite BP control was also demonstrated in the Strong Heart Study (SHS), an unselected population-based cohort with high prevalence of obesity and diabetes mellitus. In that context, even LVMI increased over time, likely due to the high prevalence of obesity of the SHS population, a condition that can increase the LVM progression.

The critical role of SBP control in regression of TOD has been recently pointed out in many clinical trials, but in clinical practice, the presence of cofactors could be an important determinant of the control of the atherosclerotic process and of the regression of TOD.

In our analysis, the progression of carotid atherosclerosis is independent of both SBP target and prescribed antihypertensive meds. A previous analysis from our registry demonstrated that the development of a new carotid plaque did not depend on BP control, confirming that, in this setting, the progression of vascular disease is not influenced by BP control alone, but might be influenced by other aspects of the clinical presentation. In our cohort, progression of carotid atherosclerosis could be partially explained by different type of meds prescribed. A relative small proportion of our patients were treated with calcium channel blockers, a class of medication that have been shown to be the most effective in preventing atherosclerosis progression and that we use often as third medication, explaining also why is most used in patients in the subgroup with usual SBP control, reflecting the greatest difficult to reach target BP.

Observational studies report a direct relationship between SBP level and renal disease progression. Furthermore, trials in patients with CKD showed different impact of a more intensive BP control on renal function. In the SPRINT trial, among participants without CKD at the baseline, a SBP <120 mm Hg resulted in higher rate of GFR decline than usual SBP target of 140 mm Hg. This finding is also confirmed in the post hoc analysis of the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, which includes also diabetic patients. In our analysis, tight SBP control does not worsen the progression of CKD independently of the prescribed drugs. One factor that could explain this result on the renal outcome, different from the SPRINT and the SPS3 studies, is the greater use of diuretics in the intensive-treatment group in both the cited trials, whereas in our population there are no differences in the use of diuretics in both groups.

Another aspect that needs to be recalled is that in the SPRINT study BP measurement were taken directly by unattended patients using fully automated devices, to avoid the alert reaction. As pointed out, the SPRINT SBP of 120 mm Hg may be compared to the 130 mm Hg SBP in a real life contest, where BP was measured following the current guidelines.

### STUDY LIMITATION

The CSN is an observational registry, subjected to possible bias, a limitation that is difficult to eliminate despite the extensive multivariable adjustment that we performed.
We pay particular attention to minimize both selection and observational bias, by avoiding selection of hypertensive patients seen in our network settings and applying substantially the same protocol to everyone.

In contrast with participants included in many clinical trials who often exhibit short duration of hypertension and are untreated, patients participating to the CSN have a long-lasting history of hypertension and were referred to the Hypertension Research Center after variable periods and cycles of antihypertensive treatment. In addition, in general, at the time of the first visit in our outpatient clinic, about 30% of referred patients are already in good BP control, according to current guidelines. Thus, it is likely that in many cases the maximal effect achievable with antihypertensive treatment had already been obtained in many patients, and the changes in TOD could not be expected to be substantial, when starting observations from the first visit in our outpatient clinic. We cannot determine how many patients could have had their LVMI significantly reduced before their first contact with our Center.

CONCLUSIONS

In our registry of treated hypertensive patients, the average SBP during FU does not influence the progression of TOD.

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DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

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