Clinic Versus Daytime Ambulatory Blood Pressure Difference in Hypertensive Patients

The Impact of Age and Clinic Blood Pressure

José R. Banegas, Luis M. Ruilope, Alejandro de la Sierra, Ernest Vinyoles, Manuel Gorostidi, Juan J. de la Cruz, Julián Segura, Anna Oliveras, Nieves Martell, Juan García-Puig, Bryan Williams

Abstract—Clinic blood pressure (BP) is usually higher than daytime ambulatory BP in hypertensive patients, but some recent studies have challenged this view, suggesting that this relationship is strongly influenced by age. We used the Spanish ambulatory BP monitoring cohort to examine differences between clinic and daytime BP by age among 104,639 adult hypertensive patients (office systolic/diastolic BP ≥140/90 mm Hg or treated) in usual primary-care practice, across the wide age spectrum. To assess the impact of age, cardiovascular variables, and clinic BP on the clinic–daytime BP differences, we built multivariable regression models of the average BP differences, white-coat hypertension (high clinic BP and normal daytime BP), and masked hypertension (normal clinic BP and high daytime BP). In most patients, mean clinic BP values were higher than daytime BP at all ages. Some 36.7% of patients had white-coat hypertension (amounting to 50% at clinic systolic BP of 140–159 mm Hg) and 3.9% had masked hypertension (amounting to 18% at clinic systolic BP of 130–139 mm Hg). Age explained 0.1% to 1.7% of the variance of quantitative or categorical BP differences (P<0.001). Cardiovascular variables explained an additional 1.6% to 3.4% of the variance (P<0.001). Finally, clinic BP generally explained ≥20% more of the variance (P<0.01). In this large study in usual clinical practice, clinic BP misclassified hypertension status in >40% of patients. This misclassification was not importantly influenced by age but was more evident in patients with borderline/grade 1 hypertension. These findings reinforce the importance of ambulatory BP monitoring for defining BP status in routine clinical practice. (Hypertension. 2017;69:211-219. DOI: 10.1161/HYPERTENSIONAHA.116.08567.) • Online Data Supplement

Key Words: age group ■ ambulatory blood pressure monitoring ■ conventional blood pressure ■ epidemiology ■ hypertension
with age and clinic BP values. More recently, a meta-analysis of population studies on adults and children performed in 1990 to 2009 and a recent study from the IDACO (International Database on Ambulatory Blood Pressure and Cardiovascular Outcomes) on 13 population-based cohorts have described higher clinic than daytime BP only in older subjects, but higher daytime than clinic BP in subjects under the age of 50 years. Similar results (daytime BP higher than clinic BP) have been described in children and adolescents. Most of these previous studies were centered on untreated populations, and most prior clinical studies have been small (<200 subjects). Thus, little is known about the age relationship between clinic and ambulatory BP in large cohorts of hypertensive patients in usual clinical practice, especially in primary care, where most treated and untreated hypertensive people are cared for.

In this study, we have compared clinic and ambulatory BP values across a wider age spectrum in a large cohort of >100,000 adults aged ≥18 years, attending clinics (mostly primary care) and included in the nationwide Spanish ABPM Registry. Specifically, we have described 10-year age differences in clinic versus daytime ambulatory BP in 2 ways: (1) average clinic–daytime BP differences and (2) prevalence of white-coat hypertension and masked hypertension. We explored these BP differences according to the people’s treatment status (treated or untreated). We also examine the quantitative contribution of age, cardiovascular risk factors, and clinic BP to these BP differences, which to our knowledge has not been previously assessed. This comprehensive information may help clinicians better stratify the use of ABPM to support clinical decision-making.

Methods

Study Population

The Spanish ABPM Registry was developed to promote the use of ABPM in clinical practice and is based on the distribution of >1000 ambulatory BP monitors (Spacelabs 90207) for routine use by physicians from primary care centers across Spain. Details of physicians’ recruitment and characteristics of the registry have been previously reported. Briefly, physicians and nurses received training in the use of ABPM. Consistency and quality of the information is centrally checked through an internet-based platform, using protocolized actions. International practice guidelines were used to establish general indications for ABPM. The study protocol was approved by institutional review boards from University Hospitals, and all patients gave informed consent.

In June 2015, we identified 115,708 individuals included in the Registry who had complete information regarding clinical characteristics and ABPM data of good quality. From these, 104,639 individuals were found to be hypertensive based on their clinic BP, and these individuals are the cohort for the analysis in this study.

BP Measurement

BP was measured at the clinic with validated oscillometric devices or calibrated mercury sphygmomanometers after 5 minutes of rest in a sitting position using standardized recommended procedures. Clinic BP values were calculated as the mean of 2 readings. Thereafter, 24-hour ABPM was performed using a validated, automated noninvasive oscillometric device (Spacelabs 90207; Spacelabs Inc., Redmond, WA) programmed to register BP at 20-minute intervals for the 24-hour period. Appropriate cuff sizes were used. The ABPM recordings were performed on working days, and the patients were instructed to maintain their usual activities. Valid ABPM recordings had to fulfill a series of pre-established quality control criteria, including successful recording of ≥80% of SBP and DBP during both the daytime and nocturnal periods. Daytime and nocturnal periods were defined according to the patient’s self-reported data of sleeping and waking times.

Other Study Variables

Variables collected were based on interviews and physical examination at the time of visit and on data drawn from clinical records and defined and measured in accordance with international guidelines. The variables included age, sex, weight and obesity (defined as body mass index=weight in kg/height in meters squared ≥25 kg/m²), known cardiovascular risk factors such as smoking (active use in the last year), dyslipidemia (total cholesterol ≥4.9 mmol/L, low-density lipoprotein cholesterol ≥3 mmol/L, or high-density lipoprotein cholesterol <1.0 mmol/L in men or <1.2 mmol/L in women, or fasting triglycerides >1.7 mmol/L or use of lipid-lowering drugs), diabetes mellitus (plasma fasting glucose ≥7 mmol/L or use of antidiabetic drugs), and previous cardiovascular disease as documented in the clinical record (coronary event, cerebrovascular event, heart failure hospitalization, coronary or peripheral revascularization). Details of antihypertensive treatment were also recorded.

Statistical Analysis

The 104,639 hypertensive individuals were defined as having clinic SBP ≥140 mmHg and DBP 90 mmHg or receiving treatment and classified according to their antihypertensive drug treatment status as treated hypertensives (n=70,997) and untreated hypertensives (n=33,642).

According to study descriptive objectives, we calculated (1) the mean differences between clinic BP and daytime ambulatory BP in 10-year age bands and (2) the prevalence of white-coat hypertension (clinic SBP ≥140 or DBP ≥90 mmHg and daytime SBP/DBP <135/85 mmHg) and of masked hypertension (clinic SBP/DBP <140/90 mmHg and daytime SBP ≥135 or DBP ≥85 mmHg). These estimates were compared across age, BP decile, and BP treatment status groups with analysis of variance or χ² tests as appropriate.

Next, to assess the impact of age, cardiovascular variables, and clinic BP on the differences between clinic versus daytime ABPM, we used 2 strategies: (1) graphical examination of the BP differences for individuals at all ages within the same BP decile and along the whole clinic BP continuum and (2) multivariable regression analysis in which 4 multivariable models were built with the following dependent variables: (a) multiple linear regression of average SBP and DBP differences and (b) multiple logistic regression of white-coat and masked hypertension. Cardiovascular variables considered included age decade, sex, obesity (yes/no), diabetes mellitus (yes/no), dyslipidemia (yes/no), smoking (yes/no), cardiovascular disease (yes/no), daytime heart rate, number of antihypertensive medications, and clinic SBP and DBP. To quantify the independent contribution of covariates, we calculated square R coefficients (multiple correlation for linear regression and Nagelkerke coefficient for logistic regression), which indicate the part of the variance of the dependent variable explained by covariates in the model. R² was first calculated for unadjusted age decade, then R² for the model that includes age decade plus the block of cardiovascular variables, except clinic BP, and finally, R² for the model additionally adjusted for clinic BP. Next, the change in R² before and after adjustment for covariates was determined, testing statistical significance through F ratio tests. Separate analyses were performed for men and women.

To check the reproducibility of the quantitative clinic–daytime BP differences, we ran an additional analysis on the 4720 individuals with 2 ABPM records available. We used generalized linear models with repeated measures to test statistical significance between measurements, and the results were calculated for treated and untreated hypertensive subjects. Finally, though for the purpose of the present study we focused on daytime ambulatory BP, we undertook sensitivity analyses to check the robustness of the age-related clinic–ambulatory BP differences to the use of different ambulatory BP criteria (24-hour BP of 130/80 mmHg and nighttime BP of 120/70 mmHg). The SPSS for Windows version 19.0 software (IBM, Armonk, NY) was used for statistical analysis. A 2-tailed P value <0.05 was considered to indicate statistical significance.
Results

Cohort Characteristics
Mean age of the cohort was 59.3 years (range, 18–103), 53.4% were men, mean clinic BP was 150.6/87.8 mm Hg, mean daytime BP was 133.2/79.5 mm Hg, mean daytime heart rate was 74.3 bpm, and mean body mass index was 29.9 kg/m² (Table 1). Some 67.8% of patients had treated hypertension, mean number of BP medications among treated hypertensive patients was 2.1, and 35.8% of patients were receiving monotherapy. Mean age of treated hypertensive patients was 61.8 years (52.5% men) and that of untreated hypertensive patients was 54.0 years (55.5% men).

Differences Between Clinic and Daytime Ambulatory BP by Age
In the whole hypertensive cohort and in the 2 BP treatment groups, mean clinic SBP and DBP were usually significantly higher than their mean daytime BP counterparts within each age group (P<0.05; Table 2).

In general, the unadjusted magnitude of the mean clinic–daytime BP difference increased significantly with age, more consistently from age 30 to age 80 years (P<0.001).

Relation Between the Clinic–Daytime BP Difference and Clinic BP
The range of variation in BP differences among age decades for each clinic BP decile was much narrower than the range of variation in BP differences along the clinic BP continuum (Figure). These data indicate a greater influence of clinic BP versus age on BP differences. In general, among treated and untreated hypertensive patients, clinic BP values tended to be higher than daytime BP values. This was true for >95% of subjects and above a clinic BP value of ≈120/75 mm Hg (Figure). Below this clinic BP threshold, clinic BPs were predominantly lower than daytime BP values.

Prevalence of White-Coat and Masked Hypertension
The frequency of white-coat hypertension was 36.7%, amounting to 52.7% in those at SBP of 140 to 149 mm Hg (49.5% within SBP 140–159 mm Hg), and generally increased with age and decreased with clinic SBP (Tables 3 and 4). The frequency of masked hypertension was 3.9%, amounting to 23% in those treated with a clinic SBP of 130 to 139 mm Hg, and generally decreased with age and increased with clinic SBP. Thus, misclassification of hypertension status by clinic BP alone was over 40%.

Multivariable Analyses of Differences in Clinic Versus Daytime Ambulatory BP
Age, cardiovascular risk variables, and clinic BP were significantly associated with all the clinic–daytime BP differences outcomes (mean SBP and DBP differences, white-coat hypertension, and masked hypertension) in univariate analyses (P<0.001). As indicated by the R² coefficients, unadjusted age decade only explained 0.1% to 1.7% of the variance of quantitative or categorical clinic versus daytime BP differences (P<0.001; Table 5). When cardiovascular variables were added to models, an additional 1.6% to 3.4% of the variance was accounted for (P<0.001). Finally, adding clinic BP explained 1% to 44.8% more of the variance (P<0.01). The percentage of variance of BP differences was much greater for quantitative SBP and DBP differences (48.1% and 41.7%, respectively) and was smaller for masked hypertension (24.4%) and white-coat hypertension (4%). Likewise, the gain in prediction was much greater for quantitative SBP and DBP differences (additional variance explained, 44.8% and 37.7%, respectively) and

Table 1. Cohort Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>18–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>70–79</th>
<th>80–89</th>
<th>≥90</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>104639</td>
<td>2373</td>
<td>6168</td>
<td>16515</td>
<td>25912</td>
<td>27090</td>
<td>20604</td>
<td>5727</td>
<td>250</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>59.3±13.7</td>
<td>24.5±3.6</td>
<td>35.3±2.8</td>
<td>45.1±2.8</td>
<td>54.7±2.9</td>
<td>64.3±2.9</td>
<td>74.1±2.8</td>
<td>82.7±2.4</td>
<td>92.0±2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men, %</td>
<td>55.917 (53.4)</td>
<td>1632 (68.8)</td>
<td>3784 (61.3)</td>
<td>9926 (60.1)</td>
<td>14766 (57.0)</td>
<td>14541 (53.7)</td>
<td>9084 (44.1)</td>
<td>2112 (36.9)</td>
<td>72 (28.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.9±6.7</td>
<td>28.0±7.1</td>
<td>29.2±6.8</td>
<td>29.7±6.8</td>
<td>30.1±6.8</td>
<td>30.3±6.6</td>
<td>30.1±6.6</td>
<td>29.2±6.4</td>
<td>28.9±7.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>16440 (15.7)</td>
<td>482 (20.3)</td>
<td>1601 (26.1)</td>
<td>4573 (27.7)</td>
<td>5448 (21.0)</td>
<td>3077 (11.4)</td>
<td>1115 (5.4)</td>
<td>144 (2.3)</td>
<td>4 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>21256 (20.3)</td>
<td>116 (4.9)</td>
<td>408 (6.6)</td>
<td>1587 (9.6)</td>
<td>4402 (17.0)</td>
<td>7115 (26.3)</td>
<td>6105 (29.6)</td>
<td>1478 (25.8)</td>
<td>45 (18.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>44458 (41.2)</td>
<td>258 (10.9)</td>
<td>1398 (22.7)</td>
<td>5291 (32.0)</td>
<td>11070 (42.7)</td>
<td>13368 (49.3)</td>
<td>10421 (50.6)</td>
<td>2549 (44.5)</td>
<td>103 (41.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVD, %</td>
<td>12450 (11.9)</td>
<td>49 (2.1)</td>
<td>182 (3.0)</td>
<td>728 (4.4)</td>
<td>2169 (8.4)</td>
<td>3521 (13.0)</td>
<td>4142 (20.1)</td>
<td>1585 (27.7)</td>
<td>74 (29.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Untreated hypertension, %</td>
<td>33642 (32.2)</td>
<td>1702 (71.7)</td>
<td>3416 (55.4)</td>
<td>7350 (44.5)</td>
<td>9150 (35.3)</td>
<td>7179 (26.5)</td>
<td>3934 (19.1)</td>
<td>874 (15.3)</td>
<td>37 (14.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treated hypertension, %</td>
<td>70997 (67.8)</td>
<td>671 (28.3)</td>
<td>2752 (44.6)</td>
<td>9165 (55.5)</td>
<td>16762 (64.7)</td>
<td>19911 (73.5)</td>
<td>16670 (80.9)</td>
<td>4853 (84.7)</td>
<td>213 (85.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of BP meds among treated</td>
<td>2.1</td>
<td>1.5</td>
<td>1.7</td>
<td>1.8</td>
<td>2.0</td>
<td>2.2</td>
<td>2.3</td>
<td>2.3</td>
<td>2.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results are presented as means (±SD) or percentage (in parentheses). BMI indicates body mass index; CVD, cardiovascular disease; and No. of BP meds, mean number of blood pressure medications.
notably smaller for white-coat hypertension. Nevertheless, even for white-coat hypertension, the contribution of clinic BP (1%) was slightly greater than that of age (0.4%). These results were similar between sexes (data not shown).

Reproducibility Analyses and Sensitivity Analyses

Plots depicting clinic–daytime BP differences by age and clinic BP in patients undergoing 2 ABPM sessions (median interval, 5 months) were almost superimposable (Figure S1 in the online-only Data Supplement). P values for BP differences between visits allowing for age decade and clinic BP levels were 0.503 for SBP and 0.200 for DBP. Results of patients untreated or treated in both visits were also reasonably reproducible (P=0.634 for SBP and 0.323 for DBP; and 0.376 for SBP and 0.204 for DBP, respectively).

When the 24-hour BP value (or nighttime BP) was used instead of daytime BP, the magnitude of the BP differences was higher because nighttime values were also taken into account, but the directions of trends of 24-hour and nighttime BP with age were the same as those of daytime BP. Also,
multivariable models of the clinic–24-hour (or nighttime) BP differences showed, similarly to the daytime BP–based models, a higher impact of clinic BP than age. Finally, whether either daytime or nighttime BP is used, masked hypertension was highest among patients at clinic SBP of 130 to 139 mm Hg, and white coat hypertension was highest in patients with SBP of 140 to 149 mm Hg.

**Discussion**

This large primary care–based study of hypertensive patients examined differences in clinic versus daytime ambulatory BP as continuous and categorical phenomena, and we show that mean clinic BP values are usually higher than their corresponding daytime ABPM-averaged values across a wide range of ages and BP treatment status (treated or untreated). Importantly, stratification by clinic BP levels and multivariate analyses showed that clinic BP makes a much larger contribution than age and other cardiovascular risk factors to the clinic BP versus daytime ambulatory BP difference, irrespective of sex. We also show that white-coat hypertension is especially common in patients with grade 1 hypertension according to clinic BP (50%), and that the frequency of masked hypertension is commonest in patients with borderline hypertension (23% in treated patients at clinic BP 130–139 mm Hg).

**Comparison With Other Studies**

At variance with prior studies, we did not find significant changes in the direction of the mean BP differences between clinic and ambulatory BP values at any particular age, even in untreated patients. In other words, these BP differences were generally positive, that is, higher clinic than daytime ABPM values across all age groups. However, these studies did not analyze the impact of clinic BP. In some of these previous studies, higher ambulatory than clinic BP values in younger individuals were attributed, in part, to greater physical activity of these individuals during the day. We did not see this trend, and in our analysis, age was a much less important determinant of the clinic–ABPM BP difference than the baseline clinic BP, that is, the higher the clinic BP, the higher the difference, irrespective of age. One potential explanation for previous data is that the clinic BP was much lower in the younger cohorts, thereby, diminishing the BP differences.

Although some studies examined predictors of the mean clinic–ambulatory BP differences, to our knowledge, no previous studies have quantified the independent contribution of clinic BP per se. In our study, a significant quantity in prediction of BP differences was gained by adding clinic BP in multivariable models (generally ≥20% of additional variance), especially for quantitative BP differences. Clinic BP contributed only to a small additional variance of white-coat hypertension, probably related to the fact that the change in the frequency of this entity only occurred across a relatively small zone of the clinic SBP range.

**Mechanisms of the BP Differences**

Mechanisms to explain the clinic–ABPM differences are largely unknown. A popular hypothesis is the so-called alerting reaction associated with the clinical setting where BP is
Hypertension
February 2017

Table 3. Prevalence of White-Coat Hypertension and Masked Hypertension, by Age and Treatment Status

<table>
<thead>
<tr>
<th>Age, y</th>
<th>N</th>
<th>White-Coat Hypertension, %</th>
<th>Masked Hypertension, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>104 639</td>
<td>36.7 (36.4/37.0)</td>
<td>3.9 (3.8/4.0)</td>
</tr>
<tr>
<td>18–29</td>
<td>2373</td>
<td>44.8 (42.8/46.8)</td>
<td>2.1 (1.5/2.7)</td>
</tr>
<tr>
<td>30–39</td>
<td>6168</td>
<td>34.8 (33.6/36.0)</td>
<td>4.0 (3.5/4.5)</td>
</tr>
<tr>
<td>40–49</td>
<td>16515</td>
<td>31.2 (30.5/31.9)</td>
<td>4.5 (4.2/4.8)</td>
</tr>
<tr>
<td>50–59</td>
<td>25 912</td>
<td>34.6 (34.0/35.2)</td>
<td>4.0 (3.8/4.2)</td>
</tr>
<tr>
<td>60–69</td>
<td>27 090</td>
<td>39.8 (39.2/40.4)</td>
<td>3.8 (3.6/4.0)</td>
</tr>
<tr>
<td>70–79</td>
<td>20 604</td>
<td>39.9 (39.2/40.6)</td>
<td>3.6 (3.3/3.9)</td>
</tr>
<tr>
<td>80–89</td>
<td>57 277</td>
<td>36.1 (34.9/37.3)</td>
<td>4.2 (3.7/4.7)</td>
</tr>
<tr>
<td>≥90</td>
<td>25 0</td>
<td>34.0 (28.1/39.9)</td>
<td>4.8 (2.2/7.5)</td>
</tr>
</tbody>
</table>

P Value ... <0.001 <0.001

Treated hypertensive patients

<table>
<thead>
<tr>
<th>Systolic Blood Pressure, mm Hg</th>
<th>N</th>
<th>White Coat Hypertension, %</th>
<th>Masked Hypertension, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>70 997</td>
<td>34.6 (34.3/35.0)</td>
<td>5.8 (5.6/6.0)</td>
</tr>
<tr>
<td>18–29</td>
<td>671</td>
<td>30.3 (26.8/33.8)</td>
<td>7.5 (5.5/9.5)</td>
</tr>
<tr>
<td>30–39</td>
<td>27 527</td>
<td>29.1 (27.4/30.8)</td>
<td>8.9 (7.8/10.0)</td>
</tr>
<tr>
<td>40–49</td>
<td>9 165</td>
<td>28.7 (27.9/29.6)</td>
<td>8.2 (7.6/8.8)</td>
</tr>
<tr>
<td>50–59</td>
<td>16 762</td>
<td>32.6 (31.9/33.3)</td>
<td>6.2 (5.8/6.6)</td>
</tr>
<tr>
<td>60–69</td>
<td>16 670</td>
<td>37.8 (37.1/38.5)</td>
<td>4.5 (4.2/4.8)</td>
</tr>
<tr>
<td>80–89</td>
<td>48 53</td>
<td>34.2 (32.9/35.5)</td>
<td>4.9 (4.3/5.5)</td>
</tr>
<tr>
<td>≥90</td>
<td>213</td>
<td>33.8 (27.4/40.2)</td>
<td>4.9 (2.0/7.8)</td>
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</table>

P Value ... <0.001 <0.001

Untreated hypertensive patients

<table>
<thead>
<tr>
<th>Systolic Blood Pressure, mm Hg</th>
<th>N</th>
<th>White Coat Hypertension, %</th>
<th>Masked Hypertension, %</th>
</tr>
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<tbody>
<tr>
<td>All subjects</td>
<td>33 642</td>
<td>41.3 (40.8/41.8)</td>
<td>...</td>
</tr>
<tr>
<td>18–29</td>
<td>1702</td>
<td>50.5 (48.1/52.9)</td>
<td>...</td>
</tr>
<tr>
<td>30–39</td>
<td>34 16</td>
<td>39.4 (37.7/41.0)</td>
<td>...</td>
</tr>
<tr>
<td>40–49</td>
<td>7 350</td>
<td>34.2 (33.1/35.3)</td>
<td>...</td>
</tr>
<tr>
<td>50–59</td>
<td>9 150</td>
<td>38.3 (37.3/39.2)</td>
<td>...</td>
</tr>
<tr>
<td>60–69</td>
<td>7 179</td>
<td>46.3 (45.1/47.5)</td>
<td>...</td>
</tr>
<tr>
<td>70–79</td>
<td>3 934</td>
<td>48.9 (47.3/50.5)</td>
<td>...</td>
</tr>
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<td>80–89</td>
<td>8 74</td>
<td>46.3 (43.0/49.6)</td>
<td>...</td>
</tr>
<tr>
<td>≥90</td>
<td>37</td>
<td>35.1 (19.7/50.5)</td>
<td>...</td>
</tr>
</tbody>
</table>

P Value ... <0.001 ... 

Results are presented as percentages (95% confidence interval). All P values across systolic blood pressure groups were <0.001.

White-coat hypertension: clinic SBP ≥140 or DBP ≥90 mm Hg and daytime ambulatory SBP/DBP <135/<85 mm Hg. Masked hypertension: clinic SBP/DBP <140/<90 mm Hg and daytime ambulatory SBP ≥135 or DBP ≥85 mm Hg. DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

measured.12,13,28 We found that clinic heart rate was significantly higher than daytime heart rate (75.5 bpm versus 74.3 bpm; P<0.001) at any age group, except the youngest, which apparently favors the alert reaction as one mechanism for the WCE. However, this effect is too small and, thus, not consistent with a major role for an alerting reaction.12,29
Unfortunately, we have no information on the level of physical activity or other factors possibly influencing the differences observed. Nevertheless, in our study, the clinic–daytime SBP differences versus clinic–nighttime SBP differences after adjusting for clinic SBP were higher among younger (<60 years) than among older subjects (14.7 versus 9.3 mm Hg; \( P < 0.001 \)), which supports the possibility that physical activity plays some role in the WCE.

With regard to the mechanisms of masked BP reactions (daytime higher than clinic BP, in particular, among hypertensives with lower clinic BP), Grassi et al.\(^30\) reported that this may be because of a marked adrenergic overdrive, and it could reflect that these patients experience autonomic calming in the clinic setting, which is lost in normal daily living.

### Clinical Implications

Our study findings are relevant for clinical practice because they reinforce the importance of ABPM, or potentially other methods such as home BP measurement\(^24\) as an alternative, for better defining BP status and classification of white-coat and masked hypertension phenomena in routine clinical practice.

Given the magnitude of white-coat hypertension (one third of all subjects), physicians could overdiagnose hypertension or inappropriately classify hypertension as more severe than it actually is, all of which could lead to overtreatment based on clinic BP alone. Moreover, for those on treatment, clinic BP will often substantially underestimate the number of patients who are truly controlled, leaving many apparently lower-risk patients at the burden of unnecessary additional BP medication. These conclusions assume that the WCE and white-coat hypertension have a benign prognosis relative to overt hypertension, warranting a conservative therapeutic approach, in the absence of compelling evidence to the contrary\(^21,32,33\)—a view not shared by everybody.\(^34\) Likewise, given the prevalence of masked hypertension (20% in treated, controlled patients), physicians will often substantially overestimate the number of patients who are truly controlled, leaving many higher risk patients at excess risk, because masked hypertension is a high-risk condition.\(^19,20,22\)

### Strengths and Limitations

A key strength of this study is that it was performed on a large single cohort of more than 100,000 hypertensive people. Although any registry study has inherent potential sources of bias, the Spanish ABPM registry provides a real-world view of clinical practice, at scale, given that primary-care physicians and patients were recruited across all the communities covered by the national healthcare system in Spain. Furthermore, we were able to show that our findings were highly reproducible in the cohort of patients with >1 ABPM measurement.

We acknowledge, however, that our study also has some limitations. Two seated BP readings from a single visit were averaged to characterize clinical BP, and the mean clinic–ambulatory BP difference could be smaller if multiple visits or more readings had been used. Nevertheless, this is a study of real clinical practice where only a few BP measurements are often recorded. Additionally, we have no way of assessing patients’ concordance with their antihypertensive treatment, and treatment could have changed between ABPM sessions.

#### Table 5. Change in Prediction of Mean Clinic Minus Daytime Ambulatory Blood Pressure Differences, White Coat Hypertension, and Masked Hypertension, by Adding in Demographic and Cardiovascular Variables and Clinic Blood Pressure

<table>
<thead>
<tr>
<th>Model</th>
<th>( R^2 )</th>
<th>Change in ( R^2 )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple linear regression of SBP differences</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted age decade</td>
<td>0.017</td>
<td>…</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for demographic and cardiovascular variables*</td>
<td>0.033</td>
<td>0.016</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additionally adjusted for clinic SBP</td>
<td>0.481</td>
<td>0.448</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple linear regression of DBP differences</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted age decade</td>
<td>0.006</td>
<td>…</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for demographic and cardiovascular variables*</td>
<td>0.040</td>
<td>0.034</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additionally adjusted for clinic DBP</td>
<td>0.417</td>
<td>0.377</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple logistic regression of white-coat hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted age decade</td>
<td>0.004</td>
<td>…</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for demographic and cardiovascular variables*</td>
<td>0.030</td>
<td>0.026</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additionally adjusted for clinic SBP and DBP</td>
<td>0.040</td>
<td>0.010</td>
<td>0.004</td>
</tr>
<tr>
<td>Multiple logistic regression of masked hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted age decade</td>
<td>0.001</td>
<td>…</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for demographic and cardiovascular variables*</td>
<td>0.035</td>
<td>0.034</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additionally for clinic SBP and DBP</td>
<td>0.244</td>
<td>0.209</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\( R^2 \) is multiple correlation coefficient for linear regression models or Nagelkerke coefficient for logistic regression models and expresses % of variation in outcome (mean clinic–daytime BP differences, white-coat hypertension, or masked hypertension) accounted for by covariates in each model. Change in \( R^2 \): increase in \( R^2 \) when the second block of covariates (demographic and cardiovascular variables) or when the third covariate (clinical BP) entered into the model. White-coat hypertension: clinic SBP \( \geq 140 \) or DBP \( \geq 90 \) mm Hg and daytime ambulatory SBP/DBP \( <135/\leq85 \) mm Hg. Masked hypertension: clinic SBP/DBP \( \geq 140/\geq90 \) mm Hg and daytime ambulatory SBP \( >135 \) or DBP \( >85 \) mm Hg. BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*Adjusted for age decade, sex, obesity, diabetes mellitus, dyslipidemia, smoking, cardiovascular disease, daytime heart rate, and number of BP medications.

Although our results could in part be related to regression-to-the-mean because the mean BP differences were increasing with increasing clinic BP values, there was a wide range of BP differences in different individuals with the same clinic BP value, making this explanation unlikely. Furthermore, there was a good medium-term reproducibility of the magnitude and age trends in the WCE according to clinic BP, which argues against regression-to-the-mean playing a major role in the WCE.

Finally, the possibility of different levels of daily-life stressor, such as physical activity, could also be an important mechanism accounting for the clinic BP–ABPM differences.
over time; nevertheless, medium-term reproducibility was striking in untreated subjects.

Perspectives
In a large cohort of 104639 hypertensive patients seen in usual clinical practice, we first show that daytime ambulatory BP was generally lower than clinic BP at all ages, and clinic BP versus daytime ABPM differences are largely a function of the clinic BP. These findings were consistent throughout hypertension treatment status, reproducible in the medium term, and robust to different ambulatory BP criteria (daytime, 24-hour, or nighttime). Of practical importance, white-coat hypertension (ie, ABPM is normal) is unlikely to occur once the clinic BP is grade 2 or above and is most likely to occur in those with grade 1 hypertension. Thus, for the diagnosis of hypertension, if the availability of ABPM is restricted, then it would be best deployed to rule out white-coat hypertension in patients with grade 1 hypertension according to clinic BP. Conversely, masked hypertension is more likely to occur in patients with borderline hypertension according to clinic BP. The present study also suggests that reliance on clinic BP alone is often inadequate to assess and optimize BP control because many patients have a significant white-coat or masked hypertension, leading to underestimation or overestimation of BP control, respectively. Together, these findings underscore the importance of ABPM for defining BP status in routine clinical practice. Further studies are, however, needed to assess the impact of using ABPM more widely on clinical outcomes and define the cost-effectiveness of such an approach.

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Disclosures
Members of the Spanish ABPM Registry, including some authors of this article (J.R. Banegas, L.M. Ruilope, A. de la Sierra, M. Gorostidi, J. Segura) have participated in educational meetings focused on spreading the use and importance of ABPM. Some of these meetings have been funded by Lacer Laboratories, Spain. The other authors have no relationships relevant to the contents of this article.

References


**Novelty and Significance**

**What Is New?**

- This is the largest cohort of hypertensive patients under ambulatory blood pressure (BP) monitoring worldwide that first examines in a comprehensive and quantitative way the impact of age versus clinic BP and other cardiovascular characteristics on clinic versus daytime ambulatory BP difference.

**What Is Relevant?**

- In adult hypertensive patients, clinic BP makes a larger contribution than age to the clinic BP versus daytime ambulatory BP difference.

- White coat hypertension is especially common in patients with grade 1 hypertension, and masked hypertension is commonest in patients with borderline hypertension.

**Summary**

In a cohort of 104,639 hypertensive patients, we found a clear dominance of clinic BP versus age as the main determinant of the clinic BP–ambulatory BP monitoring difference, and it has important clinical implications with regard to defining when ambulatory BP monitoring should be deployed if it is not practical to offer it universally.
Clinic Versus Daytime Ambulatory Blood Pressure Difference in Hypertensive Patients: The Impact of Age and Clinic Blood Pressure

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Clinic versus Daytime Ambulatory Blood Pressure Difference in Hypertensive Patients. The Impact of Age and Clinic Blood Pressure

BANEGAS, Running title: Clinic vs Ambulatory Blood Pressure Difference

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Figure S1. Relationship of mean clinic-diary blood pressure difference to clinic blood pressure values, among 4720 hypertensive patients with 2 ABPM examinations available. Data are mean blood pressure (BP) differences by decile of clinic blood pressure. Left panel, systolic BP in visits 1 and 2; right panel, diastolic BP in visits 1 and 2.