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*Schmieder, R.E., Schmidt, S.T., Riemer, T., Dechend, R., Hagedorn, I., Senges, J., Messerli, F.H., Zeymer, U.*

Disproportional decrease in office blood pressure (BP) compared to 24-hour ambulatory BP with antihypertensive treatment: Dependency on pretreatment BP levels

Schmieder Roland E.<sup>1</sup>, Schmidt Stephanie T. <sup>1</sup>, Riemer Thomas <sup>2</sup>, Dechend Ralf<sup>4</sup>, Hagedorn Ina<sup>5</sup>, Senges Jochen<sup>2</sup>, Messerli, Franz H.<sup>6</sup>, Zeymer Uwe<sup>2 3</sup>

<sup>1</sup> Department of Nephrology and Hypertension, University Hospital of Erlangen, Germany;

<sup>2</sup> Institut für Herzinfarktforschung Ludwigshafen, Ludwigshafen, Germany

<sup>3</sup> Medical Klinik B, Hospital of the City of Ludwigshafen, Germany;

<sup>4</sup> Department of Molecular and Clinical Cardiology Charité University Hospital Berlin, Germany;

<sup>5</sup> Clinical and Regulatory Affairs, Novartis Pharma GmbH, Nuremberg, Germany,

<sup>6</sup> Division of Cardiology, St.Luke's-Roosevelt Hospital, Columbia University, New York, USA

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Address for Correspondence and Reprint Request:  
Prof. Dr. med Roland E. Schmieder  
Department of Nephrology and Hypertension  
University of Erlangen-Nürnberg  
Ulmenweg 18  
91054 Erlangen, Germany  
Phone: +49-9131-853-6245  
Fax: +49-9131-853-6215  
E-mail: roland.schmieder@uk-erlangen.de

**Abstract:**

The long-term relationship between 24-h ambulatory BP (ABP) and office BP in patients on therapy is not well documented.

From a registry we included all patients in whom antihypertensive therapy needed to be up-titrated. Drug treatment included the direct renin inhibitor aliskiren or an ACE inhibitor (ACE-I)/angiotensin receptor blocker (ARB) or drugs not blocking the renin-angiotensin-system (RAS), alone or on top of an existing drug regimen. In all patients office BP and 24-h ABP were obtained at baseline and after 1 year with validated devices.

In the study population of 2722 patients there was a good correlation between the change in office BP and 24-hour ABP (systolic  $r=0.39$ ,  $p<0.001$ ; diastolic  $r=0.34$ ,  $p<0.001$ ). However the numeric decrease in office BP did not correspond to the decrease in ABP in a 1:1 fashion, e.g. a decrease of 10, 20 and 30 mmHg corresponded to a decrease of approximately 7.2, 10.5 and 13.9 mmHg in systolic ABP, respectively. The disproportionally greater decrease in systolic office BP compared to ABP was dependent on the level of the pretreatment BP, which was consistently higher for office than ambulatory BP. The white coat effect (difference between office BP and ABP) was on average 10/5 mmHg lower one year after intensifying treatment and the magnitude of that was also dependent on the pretreatment BP.

There was a disproportionally greater decrease in systolic office BP than in ABP, which for both office and ABP seemed to depend on the pretreatment BP level.

Keywords: office BP, ambulatory BP, antihypertensive therapy, decrease in BP, white coat effect

## Introduction

In their most recent 2013 guidelines the European Society of Hypertension and the European Society of Cardiology<sup>1</sup>. have identified lower threshold values for diagnosing arterial hypertension with 24-hour ambulatory BP (ABP) ( $\geq 130/80$  mmHg) than with office BP readings ( $\geq 140/90$  mmHg). Since 2011 the National Institute for Health and Clinical Excellence Guidance (NICE) has recommended the use of ABP monitoring to confirm the diagnosis “arterial hypertension” if office BP was  $\geq 140/90$  mmHg<sup>2</sup>. In contrast, data on target BP based on 24-hour ABP to guide antihypertensive treatment are not provided in the guidelines<sup>1</sup>. The reason seems to be that no large scale, randomized clinical trial in patients on antihypertensive treatment has been conducted to analyze the effect of antihypertensive therapy on cardiovascular prognosis with 24-hour ABP as target BP.

To develop a new consensus statement for ABP monitoring, most recently, several critical analyses of the best available evidence from clinical and observational studies were carried out<sup>3,4</sup>. The results showed that the agreement between ABP and office BP is not simply a linear and that changes in ABP do not necessarily correspond to office BP in a 1:1 fashion. However, the long-term relationship between 24-h ABP and office BP in hypertensive patients on treatment and the change of BP due to therapeutic intervention remains ill documented.

In the 3A Registry patients were prospectively followed for at least 1 year and had both office BP readings and 24-h ABP monitoring prior to and one year after intensifying antihypertensive medication to achieve target systolic office BP  $< 140$  mmHg<sup>5,6</sup>. This database represents therefore a tool allowing us to compare the changes of office BP measurements to the changes of ABP obtained under real life conditions.

## Methods

### *3A Registry*

The present analysis is based on the data of the 3A Registry<sup>6</sup>. The Registry is a prospective, observational, non-interventional, multi-centre registry listed under clinicaltrials.gov, NCT01454583 and the VfA database, a resource for non-interventional studies (<http://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/nisdb/nis-details/616>). Details of the study design and baseline data have been published in more detail elsewhere.<sup>5</sup>

In brief, consecutive patients with known or newly diagnosed arterial hypertension in whom the physician had decided independently and per best clinical judgment to initiate or intensify antihypertensive therapy were eligible for inclusion. The only exclusion criteria were participation in a randomised controlled clinical trial and foreseeable problems to perform follow-up visits. Depending on the initiated medication, patients were part of one of the three following study groups:

- 1. Treatment with the direct renin inhibitor aliskiren or
- 2. An ACE inhibitor (ACE-I) or angiotensin receptor blocker (ARB) or
- 3. Drugs not blocking the renin-angiotensin-system (Non-RAS).

Reflecting the utilised medication of the three study groups, the registry was called 3A: Aliskiren, ARB/ACE-I and others (in German called “Andere, i.e. others”). Medication was given alone or on top of an existing drug regimen.

The data were collected in web-based format with a standardised questionnaire (electronic case report form, eCRF). Measures of quality control included automated plausibility checks during data entry, queries after data entry, and in 10 % of the patients, on-site monitoring with source data verification. All data, if available, were collected during the clinical examination or from the review of the patient chart. Data were recorded at inclusion (baseline) and during follow-up visits.

### *Patients*

In 6139 patients 24-hour ABP monitoring (ABPM) was performed at baseline visit. At the 1 year examination, in 2722 hypertensive patients 24-hour ABPM was repeated in parallel to office BP measurements. Office BP was assessed with the standard devices (all were oscillometric devices) available at the physicians' office (manual sphygmomanometers or semi-automated devices), which according to German legislation must have a calibration validation. Furthermore, the German guidance for measuring office BP (sitting position, after 5 minutes of rest, at least 2 repeated measurements) had to be followed. 24-hour ABPM was also only performed with validated devices (see German guidelines: <http://www.hochdruckliga.de/blutdruckmessgeraete-mit-pruefsiegel.html>), routinely used in the respective office. Average of office BP readings and means of 24-hour ABP (minimum requirements  $\geq 50$  measurements during at least a  $\geq 22$  hour period), day-time ABP and night-time ABP were entered into the database.

Since at the time of inclusion patients had uncontrolled hypertension and the physician had decided to initiate or intensify antihypertensive therapy, we have specified the 1 year follow-up examination for our analyses when a stable situation was achieved.

### *Statistical methods*

Continuous variables were summarized with descriptive statistics (absolute numbers, means, standard deviation, or medians with 25. and 75. percentile as appropriate). Categorical data were described by the number and percentage of subjects in each category. As univariate test of location we applied the signed rank test. Statistical comparisons between groups were performed by Pearson's chi square for categorical variables, or Kruskal-Wallis test for continuous measures. Percentages were calculated on the basis of patients with data for each respective parameter. All variables showed moderate deviations from a normal distribution, as evidenced by the Kolmogorow-Smirnow-Test.

Like other biological measures, changes in both ABP and office BP may depend on baseline BP levels (Wilder Law)<sup>7</sup>. Previous analyses comparing office BP versus ABP applied a linear regression model simple statistical models<sup>8</sup>. It remains to be determined whether the relationship between office and ABP can be described by simple, proportional or linear formulas, since BP (which should not fluctuate according to the assumptions of the statistical model) is in fact a highly variable biological parameter. Thus, the statistical premises to run simple regression models are not entirely fulfilled, though widely used<sup>9, 10</sup>. Evaluating ABP and office BP by means of univariate or bivariate models hence runs the risk of inadequately simplifying a complex reality. We therefore further developed and applied a multivariate ("four-variate") model of BP change. [Details see annex 1].

We conducted all analyses with SAS 9.3 (SAS Institute, Inc., Cary, NC, USA). P-values  $\leq 0.05$  (two-sided) were considered to be significant.



## Results

### Patients' characteristics

In a total of 2722 patients office BP and 24-h ABP were obtained both at baseline and after 1 year. Clinical characteristics of the study population were: mean age 64, mean BMI 28.4 kg/m<sup>2</sup>, 45 % women, mean hypertension duration 6.9 years, average regimen 3 antihypertensive medications. Of the 2722 patients 85 % had hyperlipidemia, 14 % were current smokers, 30 % had diabetes, 31 % cardiovascular diseases and 9 % chronic kidney diseases (Table 1).

### Decrease in Office versus Ambulatory BP

In the whole study population both office BP and 24-h ABP decreased after one year of treatment. Office BP decreased by  $18.7 \pm 20 / 9.6 \pm 12$  mmHg, i.e. from  $156.2 \pm 18 / 90.6 \pm 11$  mmHg at baseline to  $137.5 \pm 14 / 81.0 \pm 8$  mmHg at one year. In parallel, 24-h ABP decreased by  $10.1 \pm 15 / 6.1 \pm 10$  mmHg, from  $146.2 \pm 15 / 85.5 \pm 11$  mmHg at baseline to  $136.2 \pm 13 / 79.4 \pm 8$  mmHg after one year. Daytime and nighttime ABP decreased accordingly (daytime from  $151 \pm 16 / 88 \pm 11$  to  $140 \pm 13 / 82 \pm 9$  mmHg; nighttime from  $136 \pm 17 / 79 \pm 12$  to  $126 \pm 15 / 73 \pm 9$  mmHg). The change in office BP and 24-hour ABP correlated highly significant with each other (systolic  $r=0.39$ ,  $p<0.001$ ; diastolic  $r=0.34$ ,  $p<0.001$ ) (figure 1). Similar correlations were observed for daytime (figure S3A and S3B) and nighttime ABP (figure S3C and S3D). However, the numeric decrease in office BP did not correspond to the decrease in ABP in a 1:1 fashion, neither for 24-h-ABP nor for daytime and nighttime ABP. For any given fall of office BP, the fall in ABP was clearly less than the one in office BP.

By applying a linear regression model, for any given pretreatment office BP (including 156/91 mmHg reflecting the average value of our population), a decrease of 10, 20 and 30 mmHg in systolic office BP corresponded to a decrease of 7.1, 10.5 and 13.9 mmHg in systolic ABP, respectively (figure 2). By applying the non-linear, multivariate additive mixed model (given for the average BP 156/91 mmHg) decreases of 10, 20 and 30 mmHg in systolic office BP corresponded to significantly smaller decreases in systolic ABP of 7.2, 10.6, and 14.0 mmHg respectively (figure 2A). Similar findings were obtained for changes in diastolic BP (figure 2B). When the analysis was repeated for daytime and nighttime ABP, a similar striking difference between the change in office versus daytime and nighttime ABP was observed (figure S4A-D). Direct comparison of the two models showed that the non-linear multivariate additive mixed model yielded even greater differences between office and ABP values than the linear regression model, in particular in the higher range of pretreatment office BP (see Annex 1, figure S1 and S2).

#### BP decrease and pre-treatment BP level

When the actually measured pretreatment office BP were stratified into 10 mmHg groups (excluding those with systolic < 140 mmHg and diastolic < 90 mmHg, respectively), the measured decrease in both office and 24 hour ABP ( in absolute terms and in percent) were highly dependent on the pretreatment BP (table 2A and B). For example, with a pretreatment systolic office BP in the range of 140 to 149 mmHg, the decrease in office and ambulatory BP were -11.3 mmHg (or -7.6 %) and -8.9 mmHg (or -5.7%), respectively (figure 3A). In contrast, with pretreatment systolic office BP  $\geq$ 180 mmHg, the decrease in office and ambulatory BP was -51.4 mmHg (or -26 %) as opposed to a decrease in ABP by -18.5 mmHg (or -11 %). Hence, the

disproportional decreases in systolic office BP compared to ABP were dependent on the pretreatment systolic BP (see table 2, irrespective whether changes are given in absolute or percent terms. A similar result was found for the relation of changes in diastolic office versus ABP (figure 2B and table 2B).

The analysis for daytime and nighttime ABP displayed similar results (table S1A-D). For example with a pretreatment systolic office BP in the range of 160 to 169 mmHg, the decrease in office and daytime ambulatory BP were -23.6 mmHg (or -14.6 %) and -13.3 mmHg (or -8.1 %), respectively (figure S4A and S4B).

#### White coat effect and pretreatment BP level

The white coat effect defined as difference between office and 24-h ABP decreased after 1 year by  $8.6 \pm 20 / 3.5 \pm 12$  mmHg (baseline:  $10 \pm 18 / 5.1 \pm 11$ , follow-up  $1.3 \pm 13 / 1.6 \pm 8.7$  mmHg,  $p < 0.001$ ). Likewise, when defined as difference between office and day time ABP, the white coat effect declined by  $7.5 \pm 20.3 / 3.2 \pm 13$  mmHg after 1 year. Interestingly, the decrease of white coat effect after 1 year was dependent on the pretreatment BP (figure 4). Thus, the observed decrease of the white coat effect contributed to the disparate changes in office BP and ABP after 1 year.

#### Discussion

Several important findings evolve from the present study. First we showed that changes in BP after initiating or up-titrating antihypertensive medication are dependent on the pre-treatment BP values. This was found to be true for both office and ABP. This phenomenon that the pre-treatment level determines to a large extent

the change per se is not restricted to change in BP only but has also been observed for changes in heart rate<sup>11</sup>, or LDL cholesterol<sup>12</sup>. The law of initial value (German: Ausgangswertgesetz) was first described by Josef Wilder in 1927 (published in 1932) who proposed that the “direction of response of body function to any agent depends to a large degree on the initial value of that function”<sup>7</sup>. However, even today it remains uncertain whether the Wilder’s law of initial value represents a real biological phenomenon or simply a statistical artifact.

From a clinical perspective, the Wilder’s law of initial value is an important concept, since it predicts that in the most severe hypertensive patients the fall in BP will be greater with the same medication than in those with less severe hypertension. If the effect were similar (i.e. the fall in BP were independent of pre-treatment level), we would encounter many more clinical complications related to hypotension with antihypertensive treatment. Wilder’s law of initial value thus indicates that we have to take the pretreatment level into account when comparing the efficacy of various antihypertensive medications in clinical trials.

Our second finding is, that change in office and ABP are not related to each other in a 1:1 fashion. When the decreases of systolic 24-hour daytime/nighttime ABP were plotted against the decrease of systolic office BP, the regression lines were not the line of identity. This observation again has important implications. Based on the average value of the pretreatment systolic BP of our population (156 mmHg), we calculated, that decreases of 10, 20 and 30 mmHg in the office systolic BP corresponded to decreases of 7.1, 10.5 and 13.9 mmHg in systolic ABP (figure 2A). The ratio between these two changes is obviously not constant; it depends on the fall in office and ABP respectively. Similar observations were also made comparing

changes in daytime and nighttime ABP with office BP changes (Figure 1 and 2). Likewise, analyzing diastolic instead of systolic BP, consistent findings were observed through with numerically lower magnitude. By using a similar approach, Mancia and colleagues documented in a meta-analysis that a fall of 10 mmHg in office systolic BP corresponded to a fall in 24-hour systolic BP to nearly the same extent, whereas a fall of 30 mmHg in office systolic BP corresponded to a fall of about 20 mmHg in ABP only<sup>4</sup>. However, a direct comparison of the 2 studies is not possible, since the basis of the analysis and pretreatment BP differed substantially between (based on mean BP of study cohorts) Mancia's metaanalysis and our large patient-based analysis.

Our third finding is that the white coat effect in patients on antihypertensive therapy decreases over time by approximately 10/5 mmHg on average, but was still present after one year. Such a decrease of the white coat effect over 1 year appeared to be dependent on pretreatment BP as well (figure 4), being negligible if pretreatment BP is close to target BP < 140/90 mmHg, but substantial with severely elevated BP values. This result is reflected by the "volatile BP component" (fig S1A and S1B dark grey column) that decreases after 1 year (fig S1A and S1B dark orange column) to a large extent if pretreatment BP is high. Thus, the greater fall in office BP in patients with severely elevated pretreatment BP is caused to large extent by the reduction of the white coat effect. Since 24-hour ABP is void of white coat and placebo effect, the changes in ABP are smaller and the pretreatment BP level lower<sup>13-15</sup>, thereby explaining at least in part why changes in office and ABP are not related to each other in a 1:1 fashion. The statistical phenomenon regression to mean might be also one contributing factor, but it is impossible to quantify the effect size from our data set.

When analyzing clinical studies with the primary objective of assessing BP changes, our findings have significant implication for their interpretation. The average systolic pre-treatment BP in the 3A Registry population was 156 mmHg and a decrease of office systolic BP of approximately 20 mmHg was observed. If we assume that the pre-treatment ABP were also 156 mmHg (in fact it was 146 mmHg), we would according to the Wilder's law of initial value expect a greater fall in ABP than the actually observed fall in ABP of 10 mmHg only.

The Symplicity-HTN 2 study illustrates the importance of our findings. Systolic BP dropped by 32/12 mmHg by office BP with pretreatment BP of 178/96 mmHg, whereas the changes in ambulatory systolic BP were 11/7 mmHg observed from a pretreatment level of 146/86 mmHg<sup>16</sup>. Similar observations were made in our 3A Registry. BP in 274 patients whose pre-treatment systolic office BP was between 170 and 179 mmHg decreased by 31 mmHg in office values but "only" 13 mmHg in ABP values.

Our study was not a randomized controlled clinical trial but the one of a non-interventional observation study which may be considered as a limitation. Both designs have their strength and weakness discussed otherwise in detail<sup>5</sup>. The use of different methods and devices for BP measurements may have created a greater variability of the results but the same device was used at baseline and after 1 year, and all devices were validated according to German legislation following the recommendations and validation according to the German Hypertension Society. Furthermore, time of office BP measurements and the peak levels of multiple drugs taken by the patients were not assessed due to the obvious inherent difficulties of

such an effort in a large-scale trial. The white coat effect was determined by the difference of office minus 24-hour or daytime ambulatory blood pressure, which represents an indirect approach of the white coat effect since the ambulatory BP measurement depends also on other factors (e.g. level of activities), which are inherent to the ambulatory BP measurements.

### Perspective

Both, changes in office BP and ABP are dependent on the pre-treatment BP level. Since the pre-treatment BP of ABP is usually lower, decreases in ABP are therefore smaller than those observed with office BP. A simple recipe to overcome these limitations in interpretation of changes in ABP is unfortunately not available due to the complexity of the phenomenon. Thus, changes in ambulatory BP in clinical studies as well as in individual patients need careful judgment and analysis bearing in mind Wilder's law of the initial value.

Disclosures:

All authors have no conflict of interest to disclose.

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## Novelty and Significance

### What Is New!

- We found a strong dependency of treatment induced changes in BP from pretreatment levels.

### What Is Relevant?

- At any given pretreatment BP we observed a disproportionately greater decrease in systolic office BP compared to ambulatory BP.
- The white coat effect was on average 10/5 mmHg lower one year after intensifying treatment and also dependent on pre-treatment BP.

### Summary

In this study cohort of 2722 patients changes in office BP were not related to changes in ambulatory BP in a 1:1 fashion. Our results should be taken into account when judging decrease in BP in individual patients and clinical studies.

**Figure Legend:**

Figure 1A: Correlation of the decrease in systolic office BP and the 24-h ABP (all patients). The regression line ( $y=4.5+0,30 x$ , where  $x$  denotes change in office BP and  $y$  change in ABP 24 means after 1 year) and its 95%CI are illustrated

Figure 1B: Correlation of the decrease in diastolic office BP and the 24-h ABP (all patients). The regression line ( $y=3.4 + 0.28 x$ , where  $x$  denotes change in office BP and  $y$  change in ABP 24 means after 1 year) and its 95%CI are illustrated

Figure 2A: BP decreases in 24-h-systolic office BP and corresponding changes in systolic ABP. BP changes have been (calculated according to the two different statistical approaches from the average pretreatment BP of our patients [156/91 mmHg]) and are given for 3 different scenarios: change in office BP -10 mmHg (A), -20 mmHg (B) and -30 mmHg (C). (ABPM 24h means (predicted by linear regr.) und ABPM 24h means (predicted by mixed model).

Figure 2B: BP decreases in 24-h-diastolic office BP and corresponding changes in diastolic ABP. BP changes have been (calculated according to the two different statistical approaches from the average pretreatment BP of our patients [156/91 mmHg]) and are given for 3 different scenarios: change in office BP -10 mmHg (A), -20 mmHg (B) and -30 mmHg (C). (ABPM

24h means (predicted by linear regr.) und ABPM 24h means (predicted by mixed model).

Figure 3: Decreases of office and ambulatory systolic 24-h-BP (measured values) categorized by pretreatment office systolic BP. (Change in office systolic BP; Change in mean of 24-h ambulatory systolic BP).

Figure 4A: Decrease of systolic white coat effect (office BP minus 24-h ABP (yellow) and office BP minus daytime BP in green) categorized by pretreatment office BP.

Figure 4B: Decrease of diastolic white coat effect (office BP minus 24-h ABP (yellow) and office BP minus daytime BP in green) categorized by pretreatment office BP.

Table1: Heterogeneity of study population

Clinical parameter	Patients with ABPM at 1 year visit (N=2722)	
age (years) (mean, quartile)	63.7 (55-71)	
female sex, % (n/N)	45 (1233/2739)	
Height, cm (mean, quartile)	170 (165-177)	
Weight, kg (mean, quartile)	84 (75-94)	
BMI, kg/m <sup>2</sup> (mean, quartile)	28.4 (25.9-31.5)	
Data about hypertension at baseline, % (n/N)		
- Recently diagnosed hypertension	12.4 (340/2739)	
- Known hypertension	87.6 (2399/2739)	
- duration of hypertension, years (mean quartile)	6.9 (2.7-12.4)	
- group with aliskiren-based treatment	69.6 (1907/2739)	
- group with ACE-I/ARB-based treatment	18.1 (496/2739)	
- group with Non-RAS-based treatment	12.3 (336/2739)	
- mean count of antihypertensive drugs	3.0	
BP data at baseline / 1 year, mm Hg (mean $\pm$ SD)	baseline	1 year
- systolic office BP	157 $\pm$ 17.9	137.5 $\pm$ 14.0
- diastolic office BP	91 $\pm$ 10.9	81.1 $\pm$ 8.2
- systolic ABP (24-hours)	146 $\pm$ 14.8	136.2 $\pm$ 12.7
- diastolic ABP (24-hours)	86 $\pm$ 10.6	79.4 $\pm$ 8.5

- systolic day-time ABP	151 ± 15.5	139.5 ± 12.5
- diastolic day-time ABP	88 ± 11.1	81.8 ± 8.7
- systolic night-time ABP	136 ± 16.9	126.4 ± 14.5
- diastolic night-time ABP	79 ± 11.5	72.6 ± 9.0

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ABP, ambulatory blood pressure; BMI, Body mass index; BP blood pressure. Quantitative values are expressed as mean and (SD) and median and (interquartiles), respectively; Qualitative variables are expressed as percentages and numbers (n/N)



Table 2A: Decrease of systolic office and 24-h-ambulatory BP (measured values) categorized by pretreatment systolic office BP

BP decrement by pretreatment systolic office BP	Change in Office BP [mmHg]		Change in ABP 24h means [mmHg]		Change in Office BP [%]		Change in ABP 24h means [%]	
	n	Mean±Std.	n	Mean±Std.	n	Mean±Std.	n	Mean±Std.
Systolic blood pressure [mmHg] (baseline)								
140-149	499	7.8±12.9	501	7.0±11.8	499	5.4±9.0	501	4.7±8.3
150-159	663	14.5±13.4	667	9.5±13.7	663	9.5±8.8	667	6.1±9.2
160-169	609	23.6±13.4	611	11.9±14.5	609	14.6±8.3	611	7.5±9.3
170-179	274	31.0±15.0	276	12.8±15.8	274	18.0±8.7	276	7.8±10.1
≥ 180	323	46.3±19.3	329	16.6±19.4	323	24.2±9.3	329	9.7±12.1
All	2368	21.7±18.9	2384	10.9±15.0	2368	12.9±10.6	2384	6.9±9.7

Table 2B: Decrease of diastolic office and 24-h-ambulatory BP (measured values) categorized by pretreatment diastolic office BP

BP decrement by pretreatment diastolic office BP	Change in Office BP [mmHg]		Change in ABP 24h means [mmHg]		Change in Office BP [%]		Change in ABP 24h means [%]	
	n	Mean±Std.	n	Mean±Std.	n	Mean±Std.	n	Mean±Std.
	Diastolic blood pressure [mmHg] (baseline)							
80-89	807	2.9±7.8	808	3.9±8.8	807	3.5±9.5	808	4.2±10.6
90-99	962	11.1±8.6	969	6.4±9.6	962	11.9±9.2	969	6.7±11.1
100-109	580	17.8±7.8	586	8.6±9.2	580	17.5±7.6	586	8.8±10.0
110-119	86	25.4±8.6	88	10.8±11.0	86	22.8±7.5	88	10.2±13.2
≥ 120	47	37.9±12.1	47	13.0±14.2	47	30.8±9.3	47	12.0±13.2
All	2482	11.0±11.0	2498	6.4±9.6	2482	11.2±10.9	2498	6.6±11.0

Please note that some patients had systolic and diastolic office BP below 140 and 80 mmHg, respectively, that explain the different total numbers of patients listed in table 2A and 2B.

Figure 1A

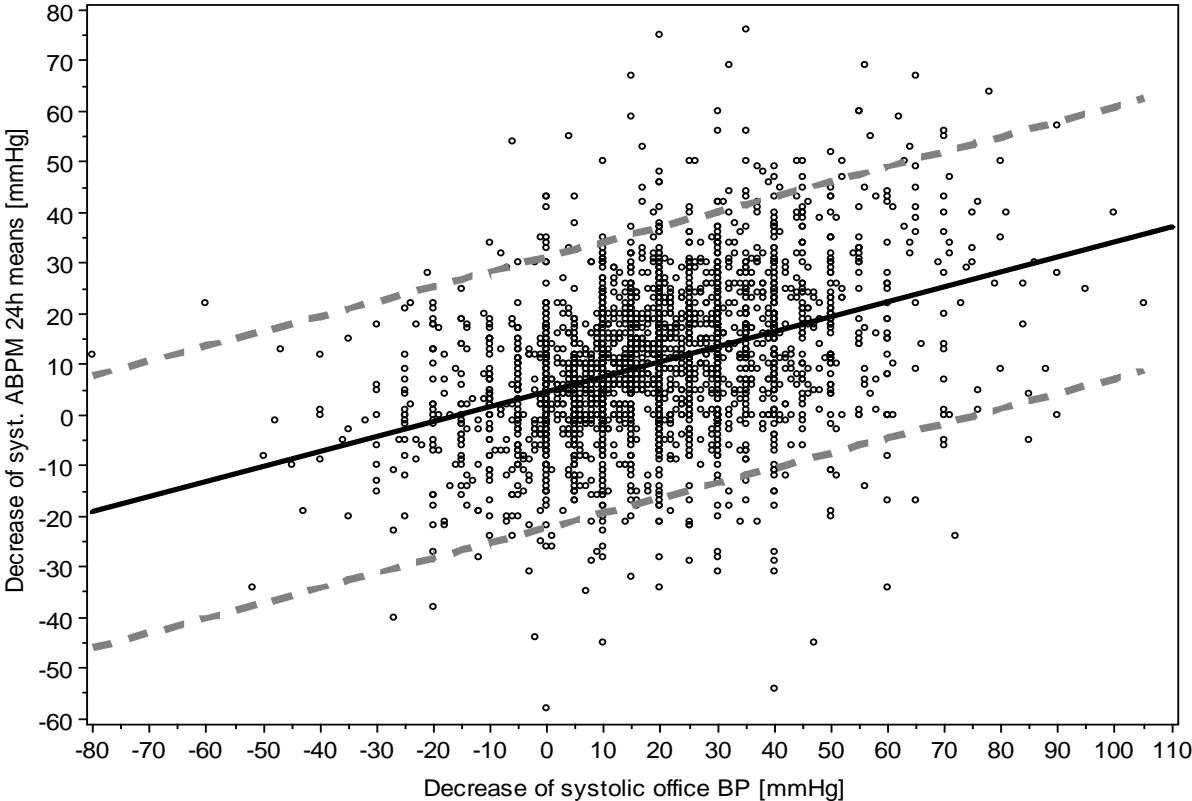


Figure 1B

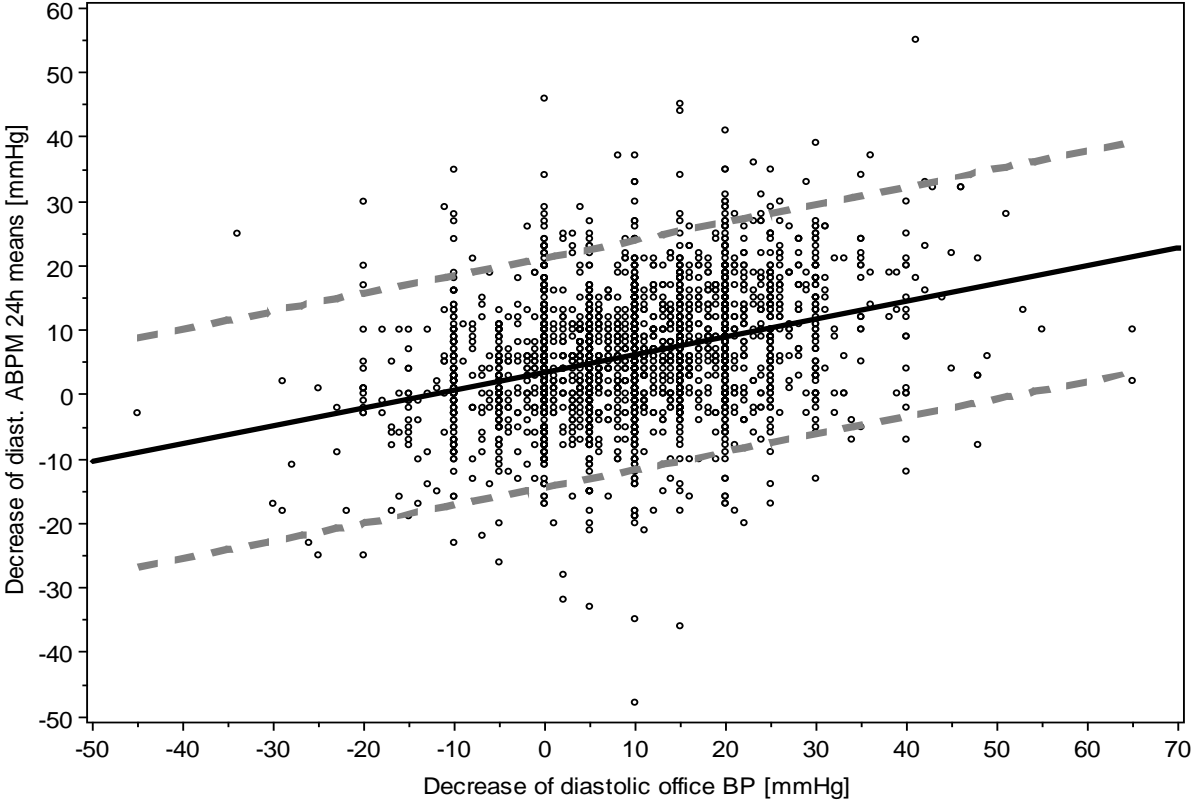


Figure 2A

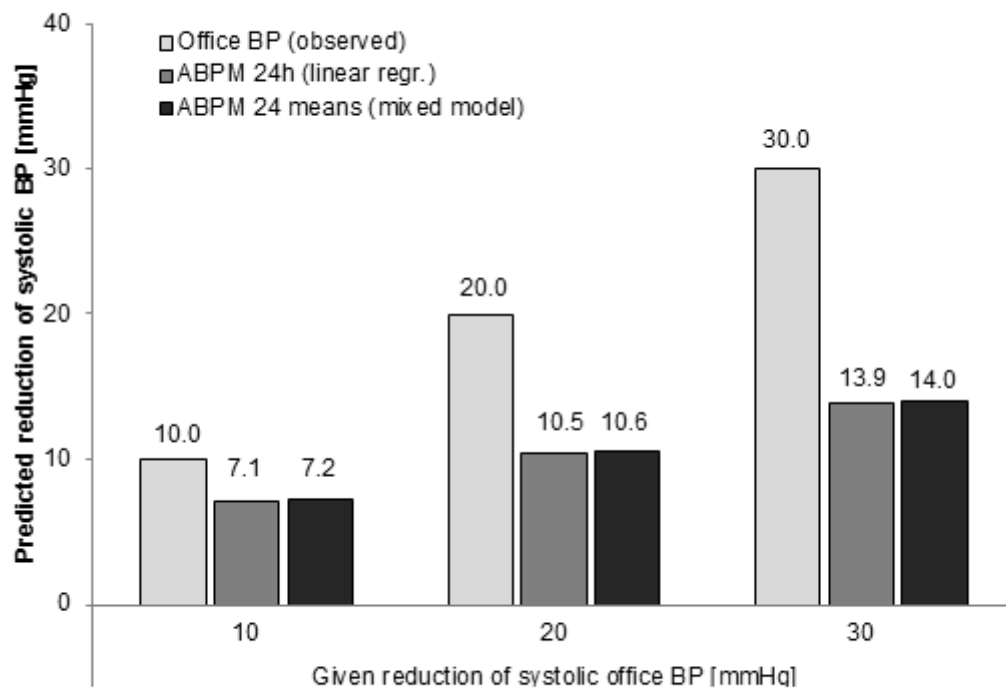


Figure 2B

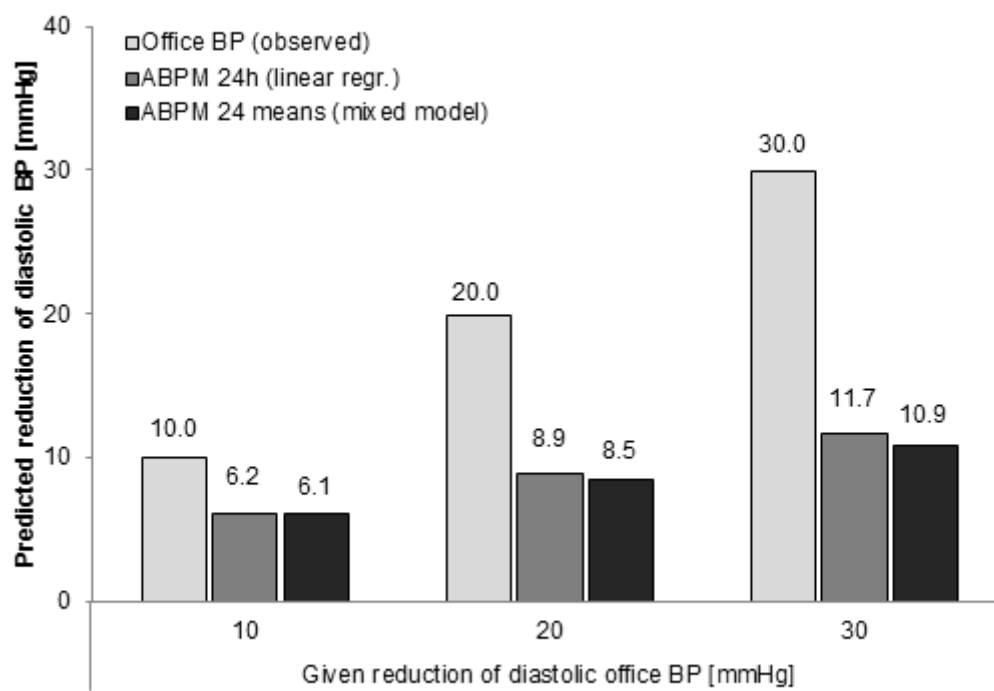


Figure 3

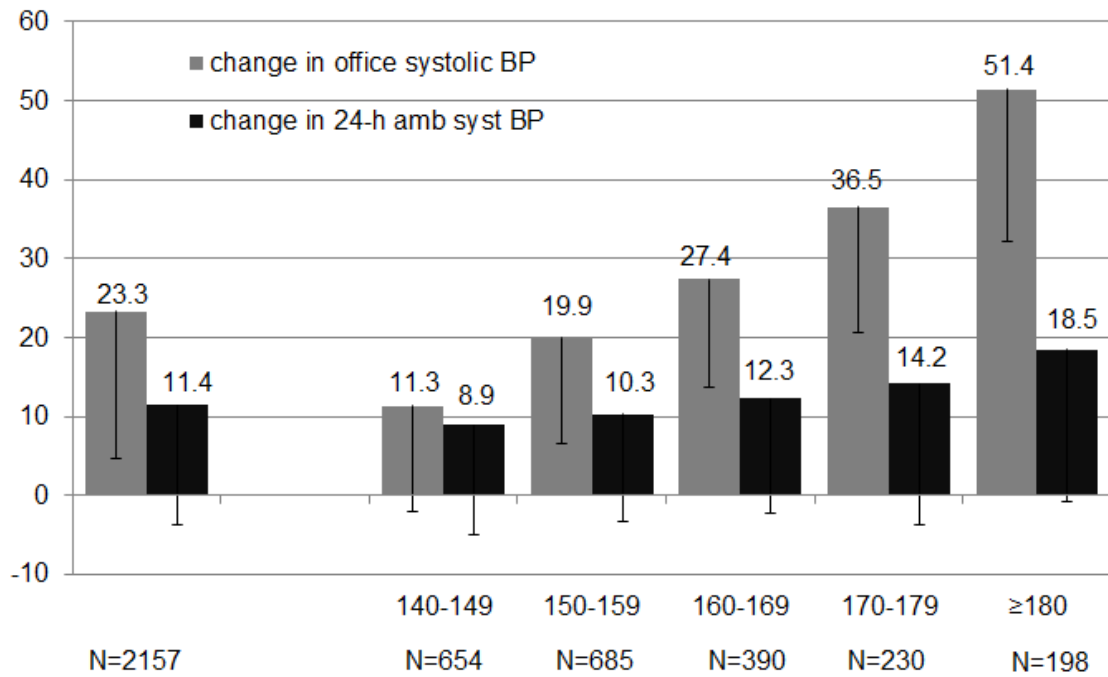


Figure 4A

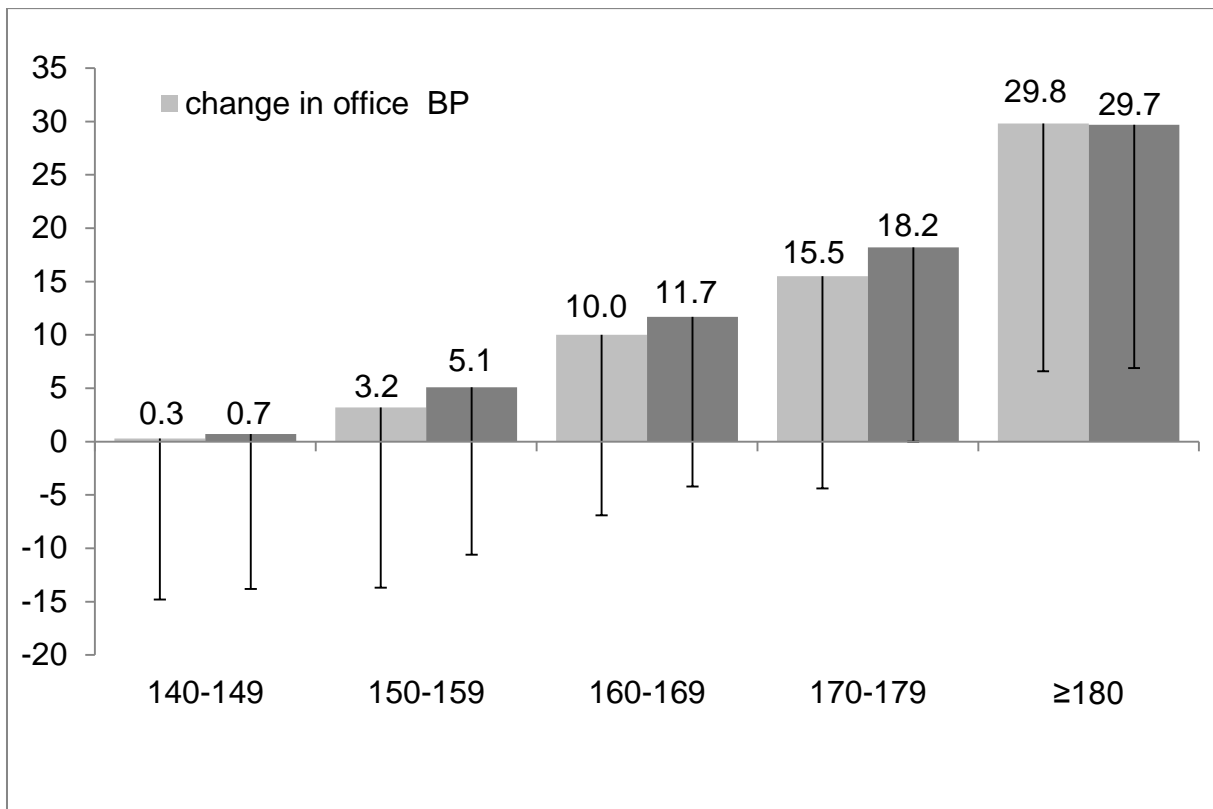
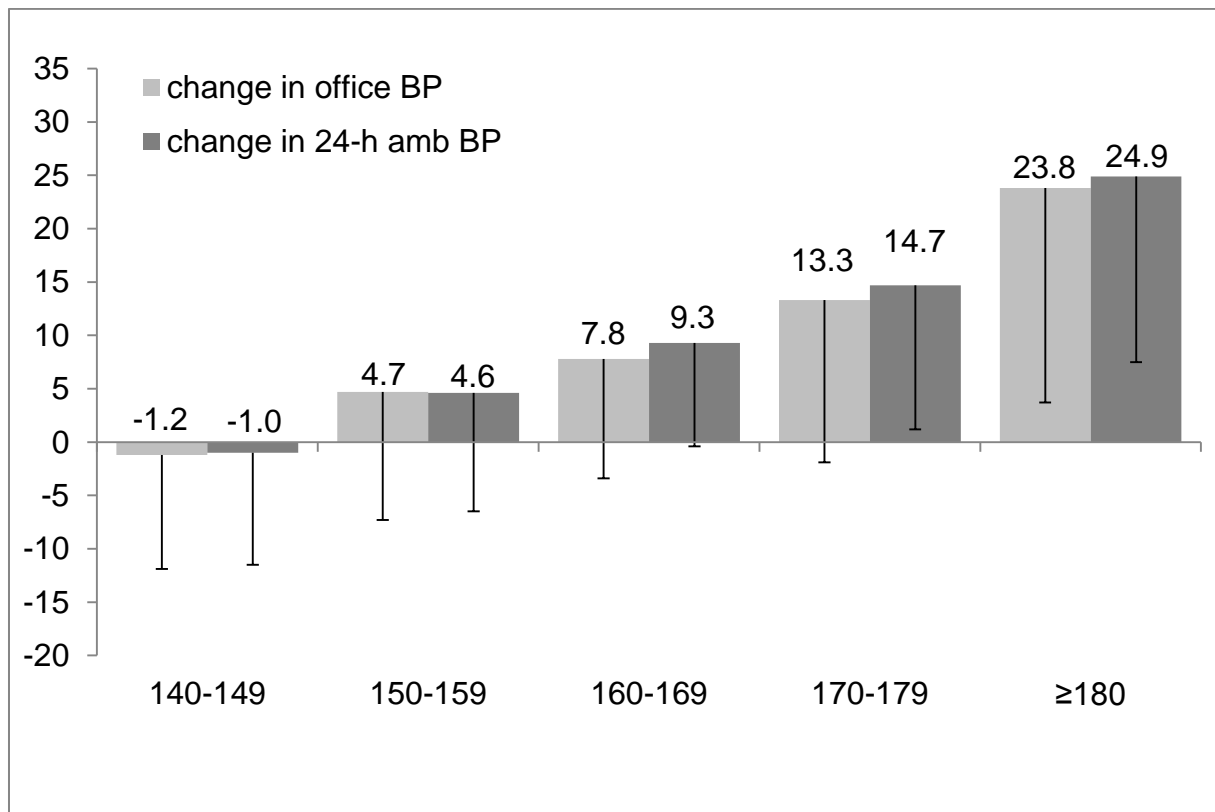


Figure 4B



Disproportional decrease in office blood pressure (BP) compared to 24-hour ambulatory BP with antihypertensive treatment: Dependency on pretreatment BP levels

Schmieder Roland E.<sup>1</sup>, Schmidt Stephanie T.<sup>1</sup>, Riemer Thomas<sup>2</sup>, Dechend Ralf<sup>4</sup>, Hagedorn Ina<sup>5</sup>, Senges Jochen<sup>2</sup>, Messerli, Franz H.<sup>6</sup>, Zeymer Uwe<sup>2,3</sup>

<sup>1</sup> Department of Nephrology and Hypertension, University Hospital of Erlangen, Germany;

<sup>2</sup> Institut für Herzinfarktforschung Ludwigshafen, Ludwigshafen, Germany

<sup>3</sup> Medical Klinik B, Hospital of the City of Ludwigshafen, Germany;

<sup>4</sup> Department of Molecular and Clinical Cardiology Charité University Hospital Berlin, Germany;

<sup>5</sup> Clinical and Regulatory Affairs, Novartis Pharma GmbH, Nuremberg, Germany,

<sup>6</sup> Division of Cardiology, St.Luke's-Roosevelt Hospital, Columbia University, New York, USA

Short Title: Disproportional decrease in office vs 24-h ambulatory BP

Address for Correspondence and Reprint Request:

Prof. Dr. med Roland E. Schmieder

Department of Nephrology and Hypertension

University of Erlangen-Nürnberg

Ulmenweg 18

91054 Erlangen, Germany

Phone: +49-9131-853-6245

Fax: +49-9131-853-6215

E-mail: roland.schmieder@uk-erlangen.de

## Online Supplemental Material

## Description of statistical models to predict changes in ABP by office BP readings

To overcome shortcoming of the classic linear regression model, we modelled the relation between baseline and follow-up of both ABP and office BP by a nonlinear, additive, mixed model. This model has advantages compared to simple models - like linear regression models or relative BP (i.e. percent) reductions - when assessing reductions of baseline values in heterogeneous patient groups. In the 3A study patients with and without cardiovascular disease, diabetes, severe hypertension, and chronic renal failure were included thereby reflecting a clinically heterogeneous population of hypertensive patients. Indeed, baseline values were very heterogeneous, as baseline ABP and office BP differed substantially between the various subgroups of patients.

We integrated four BP variables in this statistical approach and thus set up a multivariate model with four dependent variables: baseline and follow-up office BP, as well as baseline and follow-up 24-h ABP averages. Their mutual dependencies can be represented by several common and correlating BP components:

- A more in the long-term upregulated pressure (which at the end leads to the diagnosis: "hypertension") that adds to a normal value of ABP and office BP and which is usually reduced by therapy (from now on called "static pressure"),
- an additional highly "fluctuating" excess pressure (which corresponds in part to the white coat phenomenon), adding only to office BP and usually being reduced by therapy, too (from now on called "volatile pressure"),
- individual deviations (in each patient) above and below the static pressure at baseline and follow-up, which correlates between ABP mean and office BP (corresponding to the patient's stage or severity of hypertension),
- individual short-term deviations above and below the volatile excess values, at baseline and follow-up, contributing only to office BP (corresponding to the individual patient's arousal reaction).

By estimating separate reduction coefficients for static and volatile components, we were able to split reduction of office BP into a common part adding to the reduction of ABP and a more specific part belonging to office BP changes only. Figure S1A and S1B illustrates the various BP components: the common additive part and specific BP components by different shades of the colors, accordingly.

As a by-product, we obtained an estimated formula for reduction of 24h ABP means when knowing only baseline and follow-up values of office BP.

For systolic BP (mmHg) after 1y:  $Y \approx 0.280 \times X1 - 0.334 \times X2 + 12.3$

For diastolic BP (mmHg) after 1y:  $Y \approx 0.297 \times X1 - 0.238 \times X2 - 1.7$

where Y denotes ABP reduction after 1 year, X1 office BP at baseline and X2 office BP at follow-up.

We estimated all model parameters by fitting a nonlinear, multivariate, additive mixed model. In technical terms, we applied SAS procedure "nlmixed", maximizing the likelihood by a quasi-Newton algorithm and integrating over the random effects via adaptive Gauss-Hermite quadrature. Only patient records with all four variables (baseline and follow-up values for both ABP and office BP) observed entered



computations. Confidence limits for all estimates are approximate and refer to a confidence level of 95%.

Tables:

Table S1A: Decrease of systolic office and daytime ambulatory BP (measured values) categorized by pretreatment systolic office BP

BP decrement by pretreatment systolic office BP	Change in Office BP [mmHg]		Change in ABP daytime means [mmHg]		Change in Office BP [%]		Change in ABP daytime means [%]	
	n	Mean±Std.	n	Mean±Std.	n	Mean±Std.	n	Mean±Std.
Systolic blood pressure [mmHg] (baseline)								
140-149	499	7.8±12.9	477	7.3±12.7	499	5.4±9.0	477	4.7±8.6
150-159	663	14.5±13.4	631	11.1±14.5	663	9.5±8.8	631	6.9±9.6
160-169	609	23.6±13.4	582	13.3±15.9	609	14.6±8.3	582	8.1±9.8
170-179	274	31.0±15.0	267	15.5±17.9	274	18.0±8.7	267	9.0±11.0
≥ 180	323	46.3±19.3	318	16.2±20.2	323	24.2±9.3	318	9.2±12.2
All	2368	21.7±18.9	2275	12.1±16.1	2368	12.9±10.6	2275	7.3±10.2

Table S1B: Decrease of diastolic office and daytime ambulatory BP (measured values) categorized by pretreatment diastolic office BP

BP decrement by pretreatment diastolic office BP	Change in Office BP [mmHg]		Change in ABP daytime means [mmHg]		Change in Office BP [%]		Change in ABP daytime means [%]	
	n	Mean±Std.	n	Mean±Std.	n	Mean±Std.	n	Mean±Std.
Diastolic blood pressure [mmHg] (baseline)								
80-89	807	2.9±7.8	763	4.1±8.9	807	3.5±9.5	763	4.3±10.5
90-99	962	11.1±8.6	921	6.2±10.5	962	11.9±9.2	921	6.2±11.8
100-109	580	17.8±7.8	567	9.9±10.5	580	17.5±7.6	567	9.7±11.0
110-119	86	25.4±8.6	84	12.1±12.8	86	22.8±7.5	84	10.9±14.0
≥ 120	47	37.9±12.1	43	14.0±17.3	47	30.8±9.3	43	12.2±15.0
All	2482	11.0±11.0	2378	6.8±10.6	2482	11.2±10.9	2378	6.7±11.6

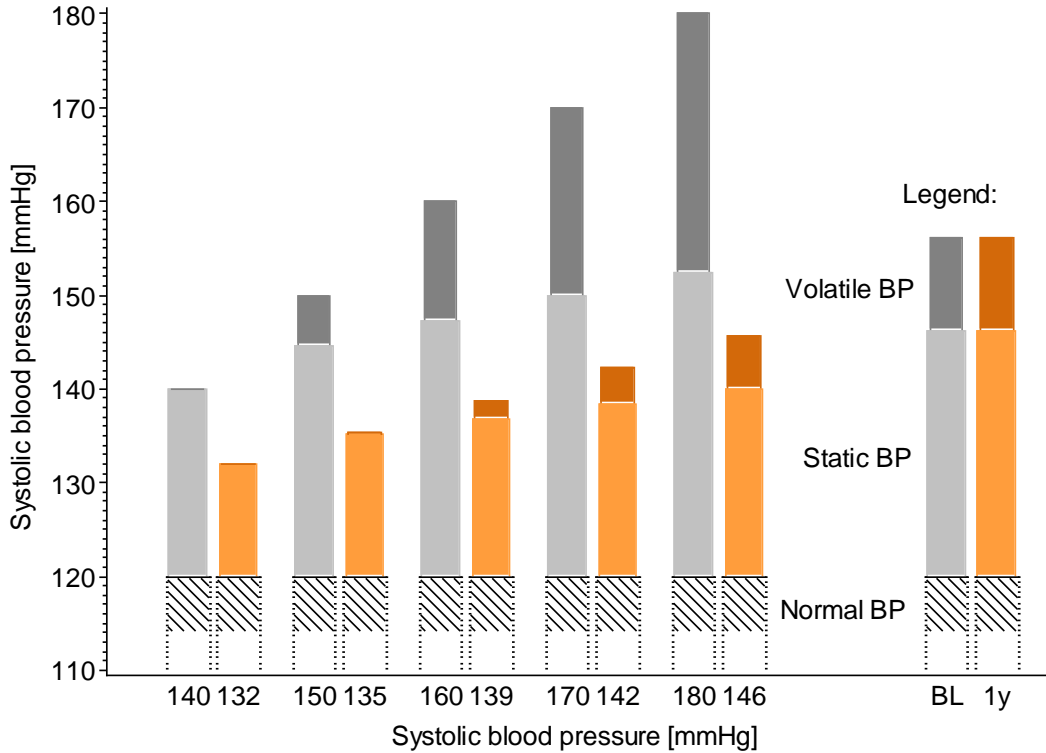
Table S1C: Decrease of systolic office and nighttime ambulatory BP (measured values) categorized by pretreatment systolic office BP

BP decrement by pretreatment systolic office BP	Change in Office BP [mmHg]		Change in ABP nighttime means [mmHg]		Change in Office BP [%]		Change in ABP nighttime means [%]	
	n	Mean±Std.	n	Mean±Std.	n	Mean±Std.	n	Mean±Std.
Systolic blood pressure [mmHg] (baseline)								
140-149	499	7.8±12.9	468	6.9±13.8	499	5.4±9.0	468	4.7±10.5
150-159	663	14.5±13.4	620	8.9±15.4	663	9.5±8.8	620	5.9±11.4
160-169	609	23.6±13.4	562	11.0±15.3	609	14.6±8.3	562	7.3±10.6
170-179	274	31.0±15.0	266	13.5±18.2	274	18.0±8.7	266	8.5±12.1
≥ 180	323	46.3±19.3	311	14.5±19.6	323	24.2±9.3	311	9.1±13.4
All	2368	21.7±18.9	2227	10.3±16.3	2368	12.9±10.6	2227	6.8±11.5

Table S1D: Decrease of diastolic office and nighttime ambulatory BP (measured values) categorized by pretreatment diastolic office BP

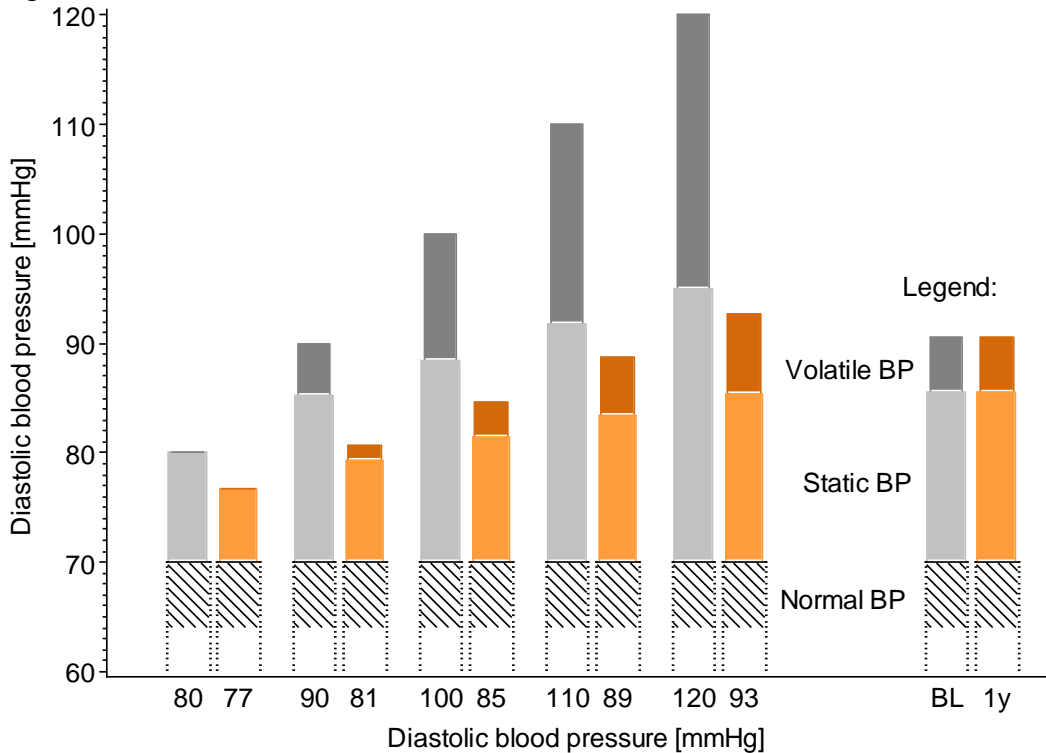
BP decrement by pretreatment diastolic office BP	Change in Office BP [mmHg]		Change in ABP nighttime means [mmHg]		Change in Office BP [%]		Change in ABP nighttime means [%]	
	n	Mean±Std.	n	Mean±Std.	n	Mean±Std.	n	Mean±Std.
Diastolic blood pressure [mmHg] (baseline)								
80-89	807	2.9±7.8	752	3.5±9.1	807	3.5±9.5	752	3.9±12.2
90-99	962	11.1±8.6	896	6.2±11.1	962	11.9±9.2	896	6.7±13.9
100-109	580	17.8±7.8	557	8.6±10.6	580	17.5±7.6	557	9.3±12.4
110-119	86	25.4±8.6	82	9.1±12.8	86	22.8±7.5	82	8.7±16.8
≥ 120	47	37.9±12.1	43	15.3±15.6	47	30.8±9.3	43	15.0±15.6
All	2482	11.0±11.0	2330	6.2±10.8	2482	11.2±10.9	2330	6.6±13.4

Figure S1A:



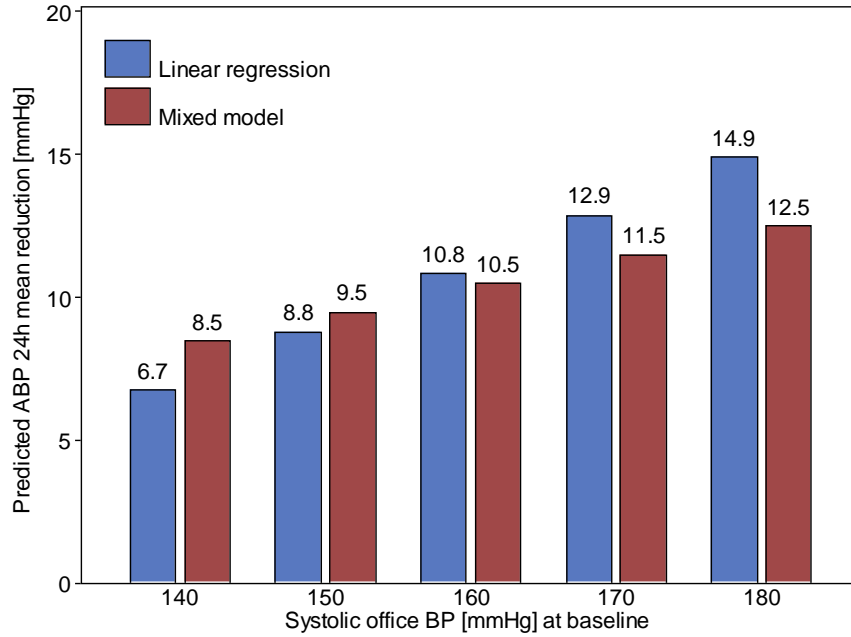
Dependency of systolic BP reduction effects of static and volatile BP components from pretreatment BP (upper part). Grey columns indicate pretreatment BP and orange columns BP after 1 year.

Figure S1B:



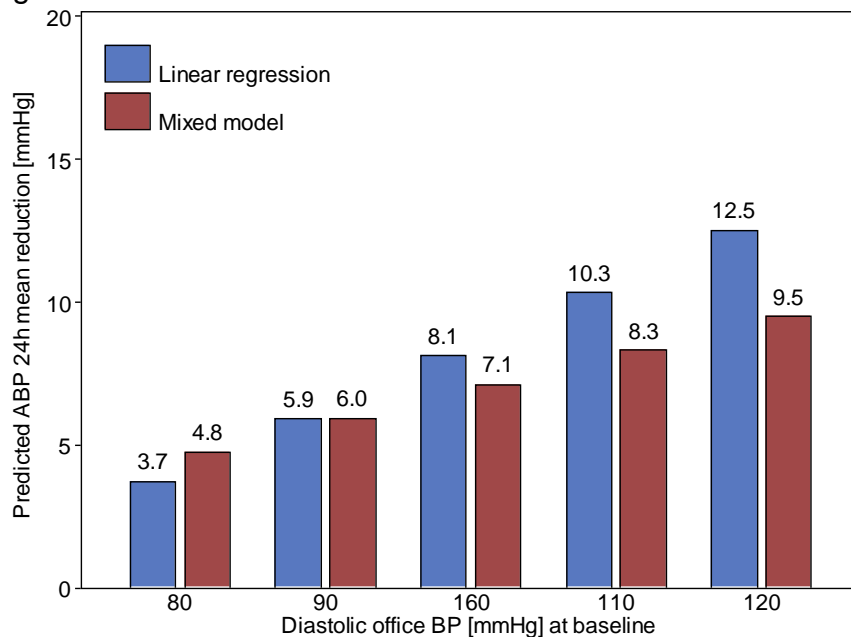
Dependency of diastolic BP reduction effects between static and volatile BP components from pretreatment BP (lower part). Grey columns indicate pretreatment BP and orange columns BP after 1 year.

Figure S2A: Systolic BP



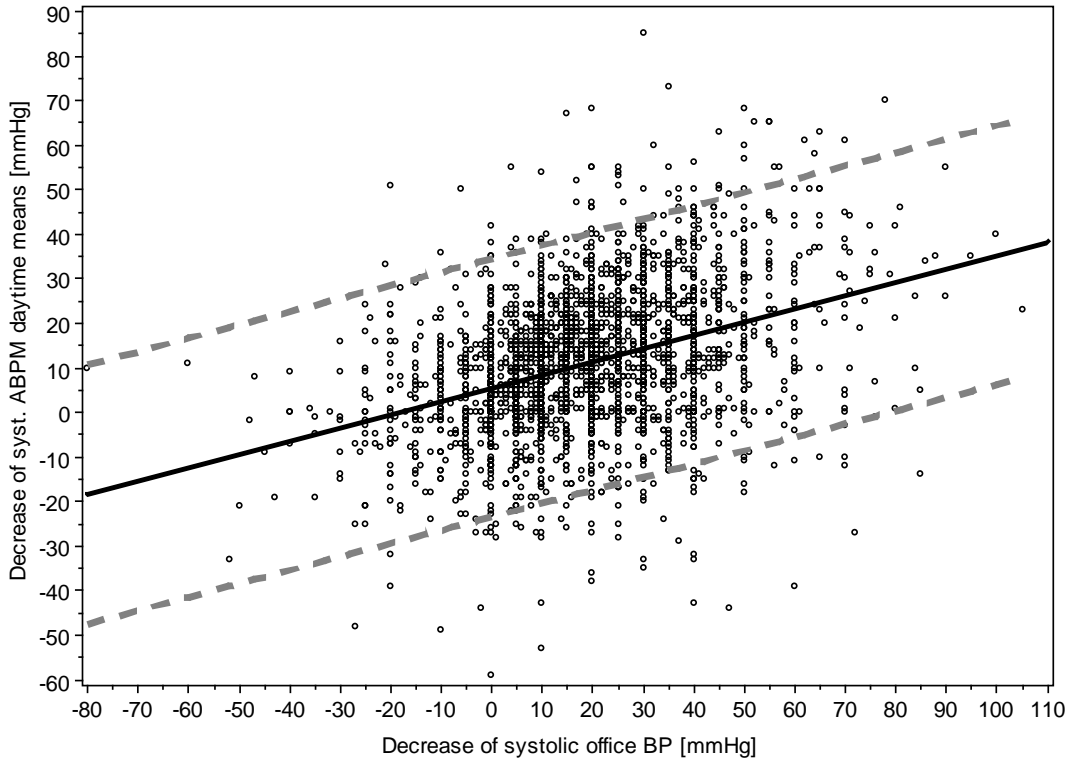
Comparison of the differences between decreases in systolic office BP minus predicted decreases in systolic ABP for various pretreatment BP derived from both the linear regression model (blue bars) versus the values derived from the non-linear multivariate additive mixed model (red bars).

Figure S2B: Diastolic BP



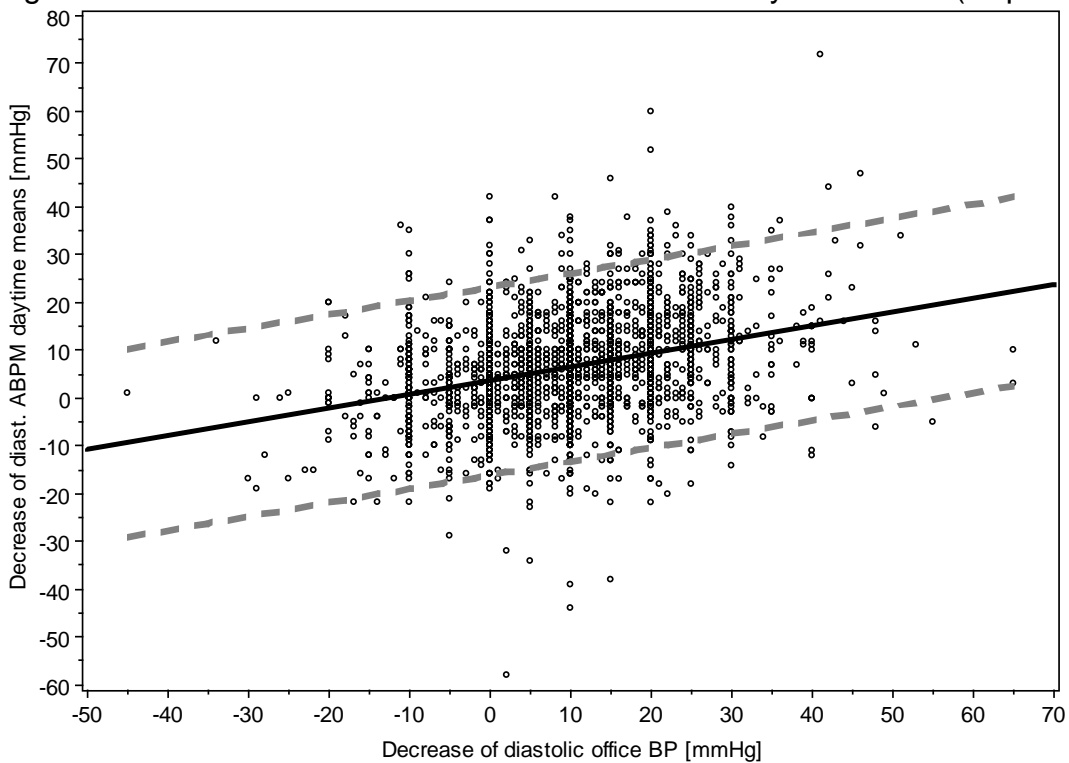
Comparison of the differences between decreases in diastolic office BP minus predicted decreases in diastolic ABP for various pretreatment BP derived from both the linear regression model (blue bars) versus the values derived from the non-linear multivariate additive mixed model (red bars).

Figure S3A: Decrease of the systolic office BP and daytime ABPM (all patients)



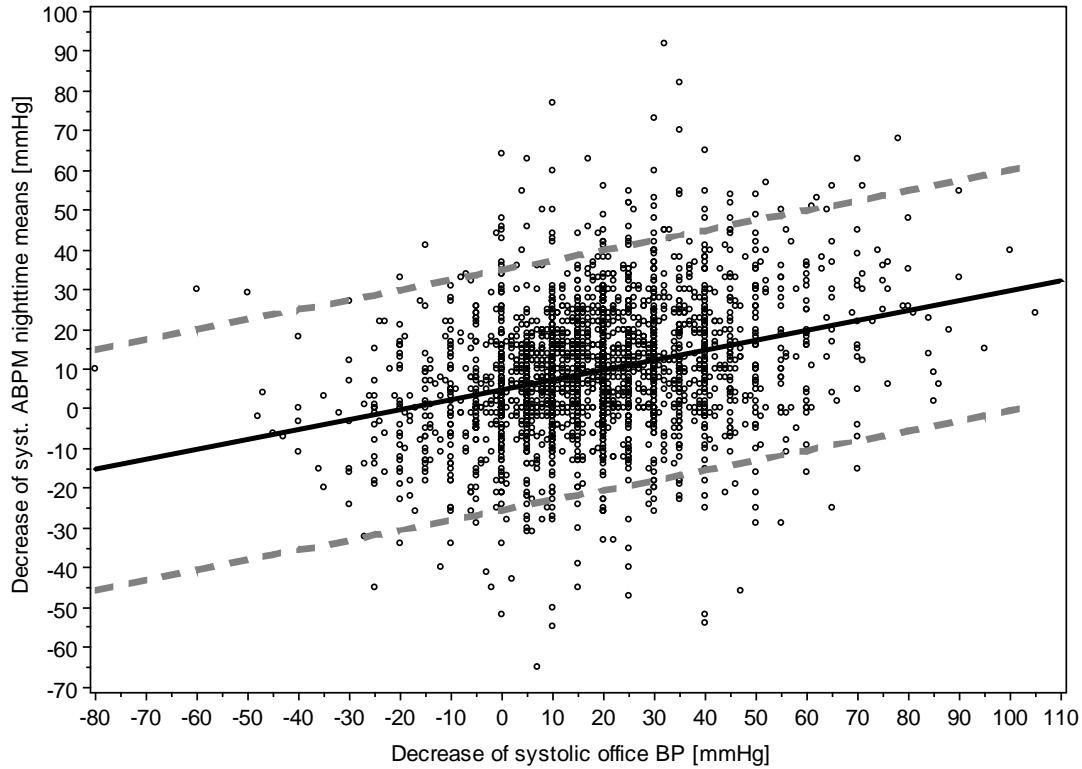
Correlation of the decrease in systolic office BP and daytime ABPM (all patients). The regression line ( $y=5.5 + 0.30 x$ , where  $x$  denotes change in office BP and  $y$  change in daytime ABPM means after 1 year) and its 95%CI are illustrated.

Figure S3B: Decrease of the diastolic office BP and daytime ABPM (all patients)



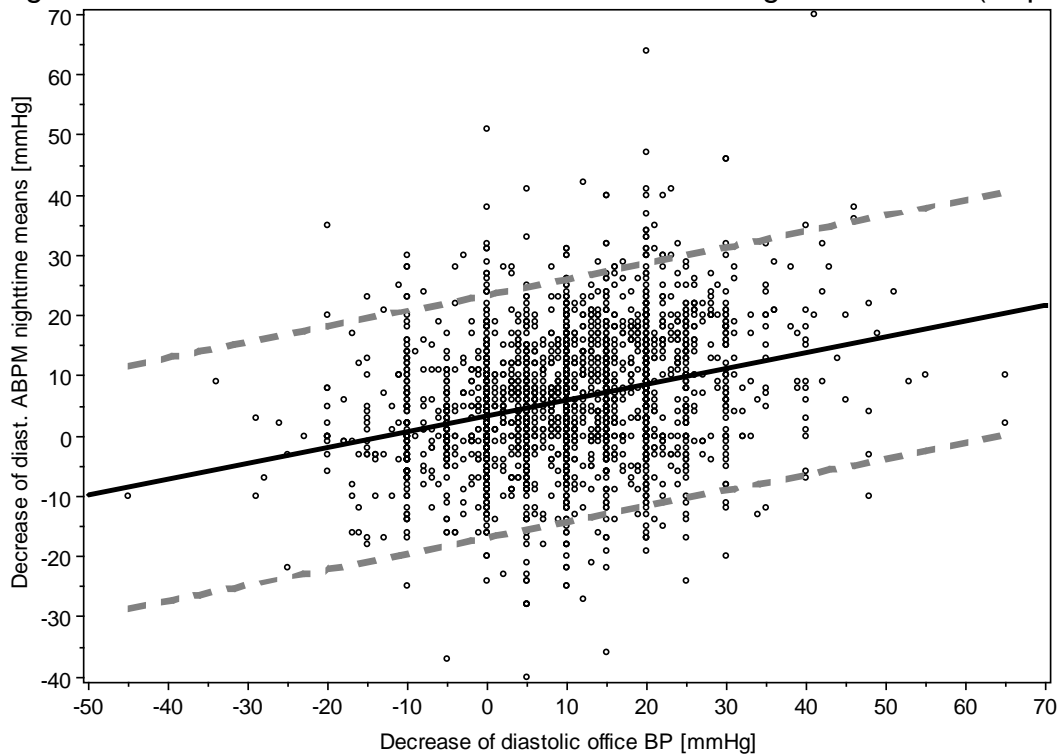
Correlation of the decrease in diastolic office BP and daytime ABPM (all patients). The regression line ( $y=3.6 + 0.29 x$ , where  $x$  denotes change in office BP and  $y$  change in daytime ABPM means after 1 year) and its 95%CI are illustrated.

Figure S3C: Decrease of the systolic office BP and nighttime ABPM (all patients)



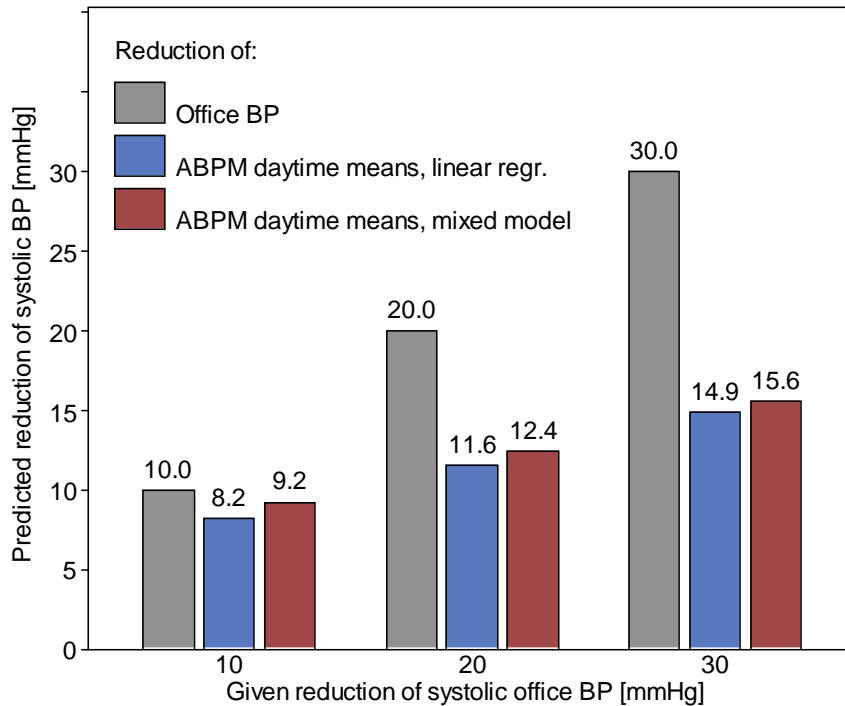
Correlation of the decrease in systolic office BP and nighttime ABP (all patients). The regression line ( $y=4.7 + 0.26 x$ , where  $x$  denotes change in office BP and  $y$  change in nighttime ABP means after 1 year) and its 95%CI are illustrated.

Figure S3D: Decrease of the diastolic office BP and nighttime ABPM (all patients)



Correlation of the decrease in diastolic office BP and nighttime ABP (all patients). The regression line ( $y=3.3 + 0.26 x$ , where  $x$  denotes change in office BP and  $y$  change in nighttime ABP means after 1 year) and its 95%CI are illustrated.

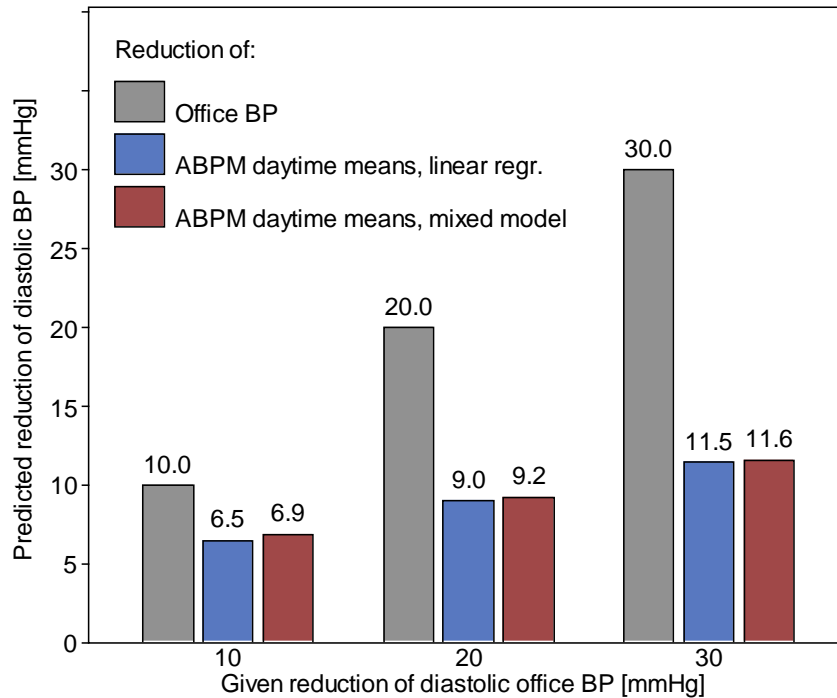
Figure S4A: BP decreases in systolic office BP and corresponding changes in daytime systolic ABP.



BP decreases in systolic office BP and corresponding changes in daytime systolic ABP. BP changes have been (calculated according to the two different statistical approaches from the average pretreatment BP of our patients [156/91 mmHg]) and are given for 3 different scenarios: change in office BP -10 mmHg, -20 mmHg and -30 mmHg. (daytime ABPM means (predicted by linear regr.) and ABPM 24h means (predicted by mixed model)).

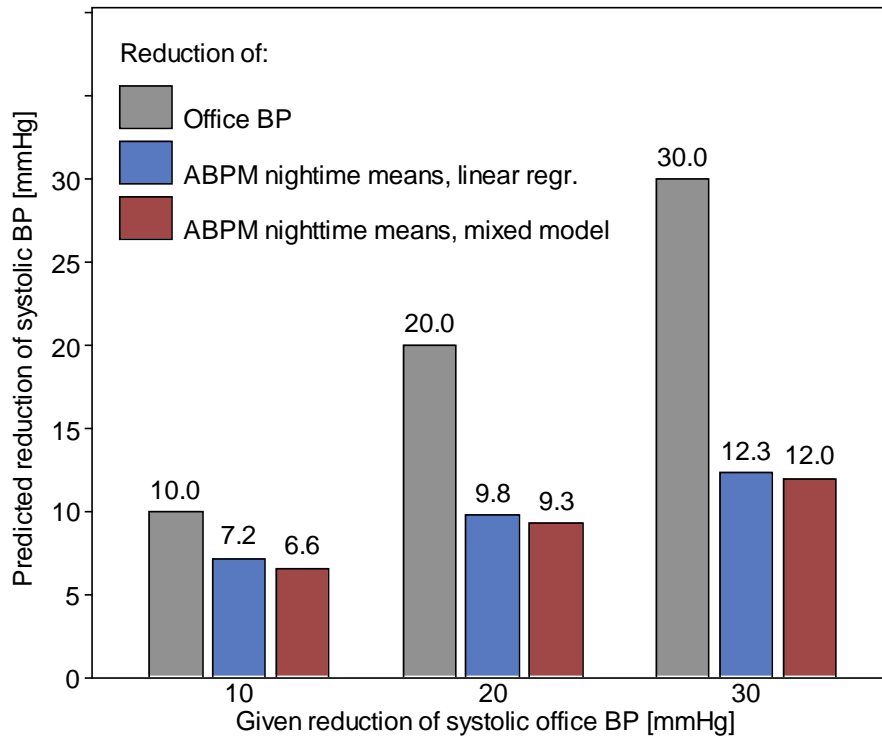


Figure S4B:BP decreases in diastolic office BP and corresponding changes in daytime diastolic ABP.



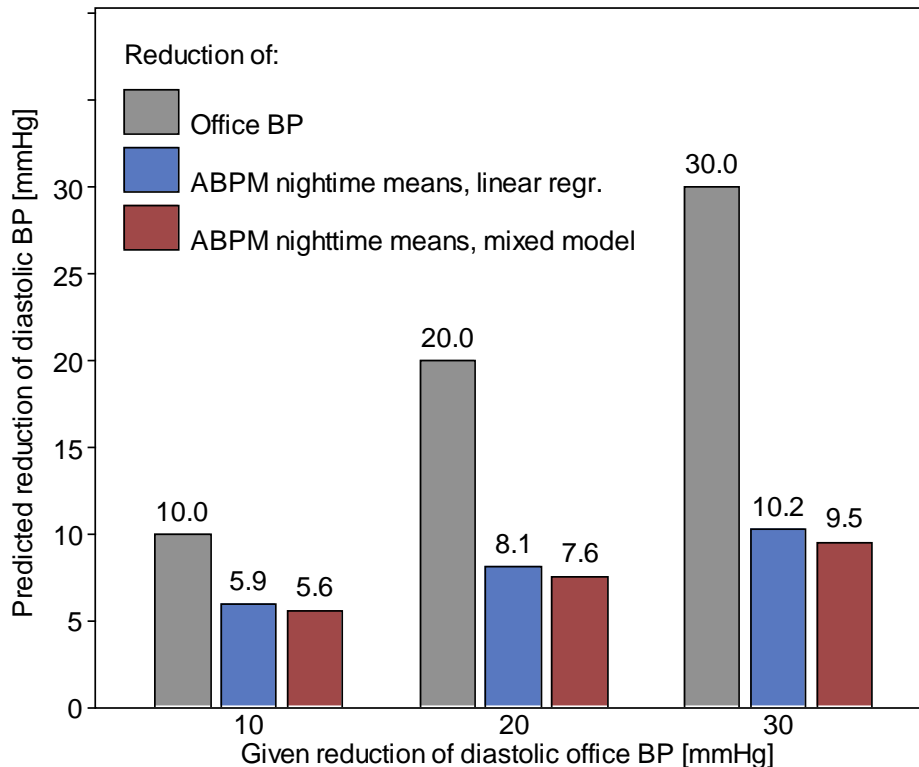
BP decreases in diastolic office BP and corresponding changes in daytime diastolic ABP. BP changes have been (calculated according to the two different statistical approaches from the average pretreatment BP of our patients [156/91 mmHg]) and are given for 3 different scenarios: change in office BP -10 mmHg, -20 mmHg and -30 mmHg. (daytime ABPM means (predicted by linear regr.) and ABPM 24h means (predicted by mixed model)).

Figure S4C: BP decreases in systolic office BP and corresponding changes in nighttime systolic ABP.



BP decreases in systolic office BP and corresponding changes in nighttime systolic ABP. BP changes have been (calculated according to the two different statistical approaches from the average pretreatment BP of our patients [156/91 mmHg]) and are given for 3 different scenarios: change in office BP -10 mmHg, -20 mmHg and -30 mmHg. (nighttime ABPM means (predicted by linear regr.) and ABPM 24h means (predicted by mixed model)).

Figure S4D: BP decreases in diastolic office BP and corresponding changes in nighttime diastolic ABP.



BP decreases in diastolic office BP and corresponding changes in nighttime diastolic ABP. BP changes have been (calculated according to the two different statistical approaches from the average pretreatment BP of our patients [156/91 mmHg]) and are given for 3 different scenarios: change in office BP -10 mmHg, -20 mmHg and -30 mmHg (nighttime ABPM means (predicted by linear regr.) and ABPM 24h means (predicted by mixed model)).