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Monotherapy Blood Pressure Response and Control Rates in Treatment-Naïve Patients with Arterial Hypertension: A Randomized Comparison of Four Different Antihypertensive Drug Classes

Annina Salome Vischer[a, b] Maria Bertsch[a, c] Vera van der Velpen[d] Franziska Küng[d] Thenral Socrates[a, b] Michael Mayr[a, b] Manuel Haschke[b, d] Thilo Burkard[a, b, e]

[a]Medical Outpatient Department and Hypertension Clinic, ESH Hypertension Centre of Excellence, University Hospital Basel, Basel, Switzerland; [b]Faculty of Medicine, University of Basel, Basel, Switzerland; [c]Medical University Clinic, Kantonsspital Baselland/Bruderholz, Bruderholz, Switzerland; [d]Clinical Pharmacology and Toxicology, Department of General Internal Medicine, Inselspital, University Hospital Bern, University of Bern, Bern, Switzerland; [e]Department of Cardiology, University Hospital Basel, Basel, Switzerland

Keywords
Arterial hypertension · Antihypertensive treatment · Angiotensin-converting enzyme inhibitor · Angiotensin receptor blocker · Calcium channel blocker · Thiazide · Thiazide-like diuretics · Ambulatory blood pressure measurement

Abstract

Introduction: Four different antihypertensive drug classes are equivalently recommended in the previous guidelines for first-line treatment of arterial hypertension (HTN). However, it is unclear, whether one of these drugs is more capable than the others to reach blood pressure (BP) control. We sought to compare response rates and BP control in these 4 classes. ***Methods:*** Patients with newly diagnosed mild to moderate HTN on 24-h BP measurements (ABPM) were randomized in a 1:1:1:1 fashion to either perindopril, olmesartan, amlodipine, or hydrochlorothiazide (HCT). ABPM was completed at baseline (BL) and after 4 weeks of half dose (treatment period 1 [TP1]). If BP control was not reached after TP1, drug dose was doubled and another ABPM completed after 4 weeks (treatment period 2 [TP2]). Patients were classified as controlled if 24-h mean BP was <130/80 mm Hg, awake BP <135/85 mm Hg, and night BP <120/70 mm Hg, and as optimal if 24-h mean BP was 115–124/65–74 mm Hg. ***Results:*** 88 patients were randomized: 20 (23%) to perindopril, 23 (26%) to olmesartan, 24 (27%) to amlodipine, and 21 (24%) to HCT. Median 24-h mean BP reduction from BL to TP1 was −11/−6 mm Hg and from TP1 to TP2 −4/−2 mm Hg. The highest BP reduction was reached with olmesartan (−15/−10 mm Hg), particularly for diastolic values, the lowest with HCT (−8/−1 mm Hg). 27% of patients reached systo-diastolic BP control, with the best control rate with perindopril and olmesartan (40 and 39%), the lowest with HCT (5%), and 21%/18% reached an optimal treatment goal

Annina Salome Vischer and Maria Bertsch contributed equally to this work.

Trial registration: www.ClinicalTrials.gov: NCT02449811, date of registration 2016-11-11, retrospectively registered.

karger@karger.com
www.karger.com/kbr

Correspondence to:
Annina Salome Vischer, annina.vischer@usb.ch

for systolic/diastolic 24-h mean values, respectively, after TP1. Three additional participants (4%) reached BP control after TP2. ***Conclusion:*** Initial antihypertensive monotherapy failed in most patients (73% uncontrolled, 21%/18% reached optimal treatment goal at TP1) even in low-risk patients, with efficacy varying by drug class (inhibitors of the renin-angiotensin-aldosterone system best, HCT least). These findings support guideline-recommended combination therapy.

Introduction

Arterial hypertension (HTN) is a major risk factor for cardiovascular (CV) morbidity and mortality [1]. Due to the aging of the population, its prevalence is constantly rising worldwide and is estimated to be around 30–45% in Europe, with a steep increase observed in the elderly [2]. Globally, more than one billion people are considered hypertensive, leading to a significant economic burden and annually approximately 10 million deaths worldwide [3]. Uncontrolled HTN results in end-organ damage, directly impacting incidence of CV events, e.g., stroke, myocardial infarction, heart failure, and peripheral artery disease [4]. More specifically, about 54% of strokes and 47% of ischemic heart disease cases are attributable to uncontrolled HTN [5].

While the 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines for the management of arterial HTN recommended an office blood pressure (BP) goal of <140/90 mm Hg for most patients, the current 2023 ESH guidelines state that reducing office BP quickly to a target of <130/80 mm Hg in most patients is key for the improvement of CV outcomes [4]. Since 2018, four major antihypertensive drug classes are equivalently recommended to treat BP to the target range: angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide/thiazide-like diuretics [4, 6]. The class of antihypertensive drug used to reach this target is considered less important than achieving the target itself [4]. In fact, the guidelines recommend initiating treatment with a two-drug combination even in treatment-naïve patients, instead of a stepped add-on approach with initial monotherapies, as was the state of the art before 2018 [7].

On level of the individual patient, the variability in the personal response may not only directly influence the adherence but also force the treating physician to change the medication [8]. Therefore, it is important to anticipate the effect of the chosen antihypertensive drug, as frequent medication changes may further reduce medication adherence [9]. Furthermore, the World Health Organization (WHO) continues to describe research gaps in the comparison of monotherapy versus combination therapy, particularly due to the absence of corresponding direct comparative studies [10]. However, to be able to plan such studies, the ideal comparators need to be selected. Despite the numerous studies that have been accomplished in the field of HTN in the last several decades, there are limited data on direct comparisons of the BP-reducing capacity of the individual classes in treatment-naïve patients.

To our knowledge, no direct comparison of the abovementioned 4 major classes exists to date in a single study, especially with the use of 24-h ambulatory blood pressure measurement (ABPM) as endpoint. The aim of this analysis was to compare BP response rates in ABPM to perindopril, olmesartan, amlodipine, or hydrochlorothiazide (HCT) in a hypothesis-generating manner.

Methods

Study Design

The methods of this trial have previously been published [11, 12]. Previously published subanalyses of this trial focused on hemodynamic profiles [11] and effects of antihypertensive treatment on the renin-angiotensin-aldosterone system (RAAS) [12]. In brief, this is an exploratory subgroup analysis of a monocentric randomized, open-label, parallel group trial designed to investigate renin-angiotensin-aldosterone peptides and hemodynamic changes after initiation of monotherapy. Patients diagnosed with primary HTN on ABPM requiring antihypertensive drug treatment were consecutively recruited from the Medical Outpatient Department at the University Hospital Basel, Switzerland, from April/2015 to March/2018. Diagnostic workup was performed according to clinical guidelines [7]. Patients with signs of secondary HTN, renal dysfunction including recipients of kidney transplants, moderate or severe hepatic impairment, clinically relevant lung disease, history of alcohol abuse, as well as pregnant or lactating patients were excluded. Patients were then randomized in a 1:1:1:1 fashion to one of the four major antihypertensive drug classes: ACEi, ARB, CCB, or thiazide diuretics and thus either to perindopril, olmesartan, amlodipine, or HCT. Patients were started on an intermediate dose of their respective antihypertensive drug (5 mg perindopril, 20 mg olmesartan, 5 mg

amlodipine, or 25 mg HCT, respectively). After 4 weeks of treatment (treatment period 1 [TP1]), another ABPM was completed. If BP control according to guidelines [7] was not reached in this ABPM, i.e., if 24-h mean BP was ≥130/80 mm Hg, awake BP ≥135/85 mm Hg, or asleep BP ≥120/70 mm Hg, antihypertensive treatment was increased to full dose (10 mg perindopril, 40 mg olmesartan, 10 mg amlodipine, or 50 mg HCT, respectively). After 4 weeks of full dose (treatment period 2 [TP2]), patients received another ABPM.

The decision to proceed to TP2 was clinically driven. The final decision, whether the dose was increased or not, was left to the patient and the treating physician. This means that some patients may have reached only partial BP control, but dose was not increased, either due to very low BP values in one part of the heart cycle and elevated BP values in the other part of the heart cycle, orthostatic symptoms, or side effects of treatment.

Trial Registration

The trial followed the ethical guidelines of the Declaration of Helsinki and the applicable International Conference on Harmonization (ICH) guidelines on good clinical practice. The trial was approved by the Local Ethics Committee (Ethics Committee of northern and central Switzerland (EKNZ) 2015-081) and registered on www.ClinicalTrials.gov (NCT02449811). All patients gave written informed consent, on which they were informed that analyses would include influences of the drugs on BP changes.

Ambulatory Blood Pressure Measurements

ABPM were usually performed using devices by Spacelabs [13] or Mobil-o-Graph [14], but in some cases by SOMNOtouch NIBP [15]. Follow-up examinations at TP1 or TP2 were performed with the same ABPM-type (cuff-based or cuffless) like at BL. All patients were asked to fill in a patients' protocol, particularly to report sleeping times. Awake and asleep periods were defined according to the patients' protocol.

HTN was defined as 24-h mean BP ≥130/80 mm Hg, awake BP ≥135/85 mm Hg, or asleep BP ≥120/70 mm Hg [4]. BP control was defined as the absence of any HTN defining BP values (i.e., 24-h mean BP <130/80 mm Hg, awake BP <135/85 mm Hg, and asleep BP <120/70 mm Hg) [4]. All values had to be below cutoff to reach the definition of BP control.

To further examine whether patients who reached BP control would reach the even stricter BP goal recommended in the 2023 ESH guidelines, and to see, how closely uncontrolled patients missed their goal, we classified the 24-h mean BP values at TP1 into categories [4]. For this, we used the equivalence values stated in the 2017 American College of Cardiology/American Heart Association guidelines and the 2024 ESC guidelines [16, 17]. Accordingly, office BP <120/70 mm Hg corresponds to 24-h mean <115/65 mm Hg, office BP 120–129/70–79 mm Hg corresponds to 24-h mean 115–124/65–74 mm Hg (i.e., the optimal treatment goal), office BP 130–139/80–89 mm Hg corresponds to 24-h mean 125–129/75–79 mm Hg, office BP 140–159/90–99 mm Hg corresponds to 24-h mean 130–139/80–85 mm Hg, and ≥160/100 mm Hg corresponds to ≥145/90 mm Hg [16, 17].

Definition of BP Response and Super Response

BP response was defined as a BP drop of ≥5 mm Hg from one period to the next. BP super response was defined as a BP drop of ≥10 mm Hg from one period to the next. The same cutoff was used for systolic and diastolic values. Systolic and diastolic values were analyzed separately.

Statistical Analyses

All results were analyzed as per protocol. Patients who did not complete the TP as foreseen by the protocol were excluded. Continuous data were displayed as median and interquartile range (IQR). Categorical data were displayed as *n* (%). Comparisons over all four groups were undertaken by using a Kruskal-Wallis test for continuous data, with a Dunn test as a post hoc test in case of significant results, and a chi-square test for categorical data, and over 2 groups by using a Mann-Whitney U test or Fisher's exact test, as applicable. Results of repeated tests were adjusted with the Bonferroni method. However, as the dependency of the parameters tested was not entirely given, considering that the four used antihypertensive drugs show different durations and modes of action, we stated the unadjusted *p* values as well to avoid both type I and II errors [18]. Prediction of BP reduction was calculated using linear regression analysis for continuous data and Kendall correlation for categorical data. A p value of <0.05 was considered as statistically significant. All statistical calculations and figures were prepared with R Version 4.3.2 [19].

Results

Baseline Characteristics

88 patients were randomized: 20 (23%) to perindopril, 23 (26%) to olmesartan, 24 (27%) to amlodipine, and 21 (24%) to HCT. 78 patients completed

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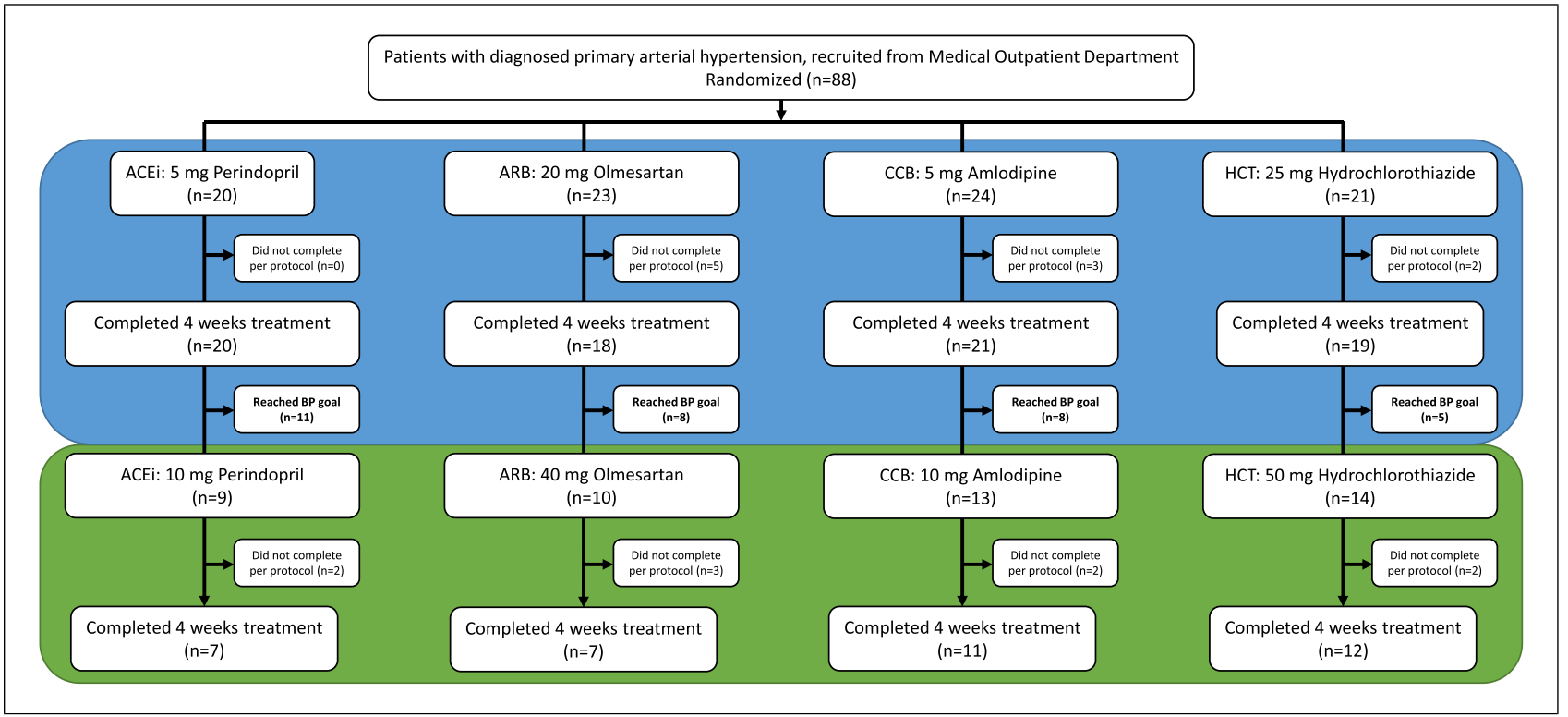


Fig. 1. Flowchart of patient inclusion and completion of treatment periods.

Table 1. Baseline characteristics for patients who completed TP1 for each medication

Baseline	Perindopril	Olmesartan	Amlodipine	HCT	*p* value
n (%)	20 (25.6)	18 (23.1)	21 (26.9)	19 (24.4)	
Female sex, *n* (%)	7 (35.0)	5 (27.8)	3 (14.3)	7 (36.8)	0.367[a]
Age, median (IQR), years	50 (38–58)	44 (32–52)	48 (37–57)	56 (45–67)	0.150[b]
BMI, median (IQR), kg/m^2	25.7 (23.8–28.0)	26.5 (22.5–29.9)	27.5 (23.8–29.2)	26.5 (24.1–29.1)	0.865°
Any comorbidities, *n* (%) Diabetes, *n* (%) Dyslipidemia, *n* (%) Rheumatological diseases, *n* (%)	7 (35.0) 1 (5.0) 2 (10.0) 1 (5.0)	4 (22.2) 1 (5.6) 1 (5.6) 2 (11.1)	2 (9.5) 0 (0) 1 (4.8) 0 (0)	6 (31.6) 2 (10.5) 3 (15.8) 1 (5.3)	0.229[a]
24-h mean sBP, median (IQR), mm Hg	138.5 (133.3–143.8)	139.5 (135.8–151.3)	138.0 (134.0–143.5)	140.0 (136.0–156.0)	0.390[b]
24-h mean dBP, median (IQR), mm Hg	86.0 (81.5–92.5)	89.0 (80.0–93.5)	89.0 (82.5–94.5)	89.0 (86.0–95.0)	0.587[b]
Awake sBP, median (IQR), mm Hg	145.5 (139.3–150.0)	145.0 (141.5–155.0)	146.0 (138.0–151.0)	146.0 (143.0–158.0)	0.423[b]
Awake dBP, median (IQR), mm Hg	90.0 (87.3–95.0)	92.5 (85.5–95.0)	96.0 (86.5–100.0)	94.0 (89.0–100.0)	0.570[b]
Asleep sBP, median (IQR), mm Hg	124.0 (117.3–130.8)	125.5 (118.0–140.8)	127.0 (119.5–129.0)	127.0 (120.0–148.0)	0.472[b]
Asleep dBP, median (IQR), mm Hg	76.5 (69.0–84.5)	77.5 (69.0–84.0)	76.0 (67.5–81.5)	81.0 (70.0–88.0)	0.571[b]

IQR, interquartile range; sBP, systolic blood pressure; dBP, diastolic blood pressure. [a]Chi-square test. [b]Kruskal-Wallis test.

TP1, and 37 patients completed TP2 (Fig. 1). Regarding patients completing TP1, median age was 49 (IQR 37–59) years, median BMI 26.5 (IQR 23.8–29.0) kg/m^2. 59 patients (76%) reported no comorbidities. Median 24-h mean systolic BP (sBP) was 139 (IQR 135–148) mm Hg, diastolic BP (dBP) was 89 (IQR 82–94) mm Hg (Table 1). There were no significant differences between the patients assigned to the 4 different medications. In the group of patients treated with perindopril and amlodipine, there was 1 patient each examined with a cuffless device, whereas in the group of patients treated with olmesartan and HCT, there were 2 patients each examined with a cuffless device (*p* value 0.823).

Blood Pressure Reduction

Median BP decrease from BL to TP1 was −10.5 (IQR [−18.8] – [−4.0])/−5.5 (IQR [−9.8] – [−1.0]) mm Hg, from TP1 to TP2 −4.0 (IQR [−11.0] – [3.0])/−2.0 (IQR [−6.0] – [1.0]]) mm Hg, for mean 24-h sBP/dBP, respectively. The median BP decreases from BL to TP1 for each randomized drug are displayed in online supplementary Table S1 (for all online suppl. material, see https://doi.org/10.1159/000545908) and Figure 2a. The median BP decreases from TP1 to TP2 for each randomized drug are displayed in online supplementary Table S2 and Figure 2b.

Unadjusted, there were significant differences between the treatments for 24-h mean dBP, awake dBP, and asleep dBP comparing over all four randomized treatments. After adjustment asleep dBP differences were significant (Fig. 2a). When comparing the effect of the individual drugs against every other drug, there were no significant differences regarding 24-h mean sBP reduction, olmesartan resulted in a significantly higher 24-h mean dBP reduction in comparison to amlodipine, which was not significant after adjustment. Unadjusted and adjusted, HCT resulted in a significantly lower 24-h mean dBP, awake dBP, and asleep dBP reduction than olmesartan (online suppl. Table S1). The distribution of the BP reduction from BL to TP1 is shown in online supplementary Figure S1. Over all four randomized treatments, there were no significant differences regarding 24-h mean, awake, and asleep sBP and dBP reduction from TP1 to TP2 (Fig. 2b and online suppl. Table S2).

Individual Blood Pressure Reduction

There were significantly less patients who were treated with HCT with a diastolic BP reduction ≥5 mm Hg in the 24-h mean values in comparison to patients treated with

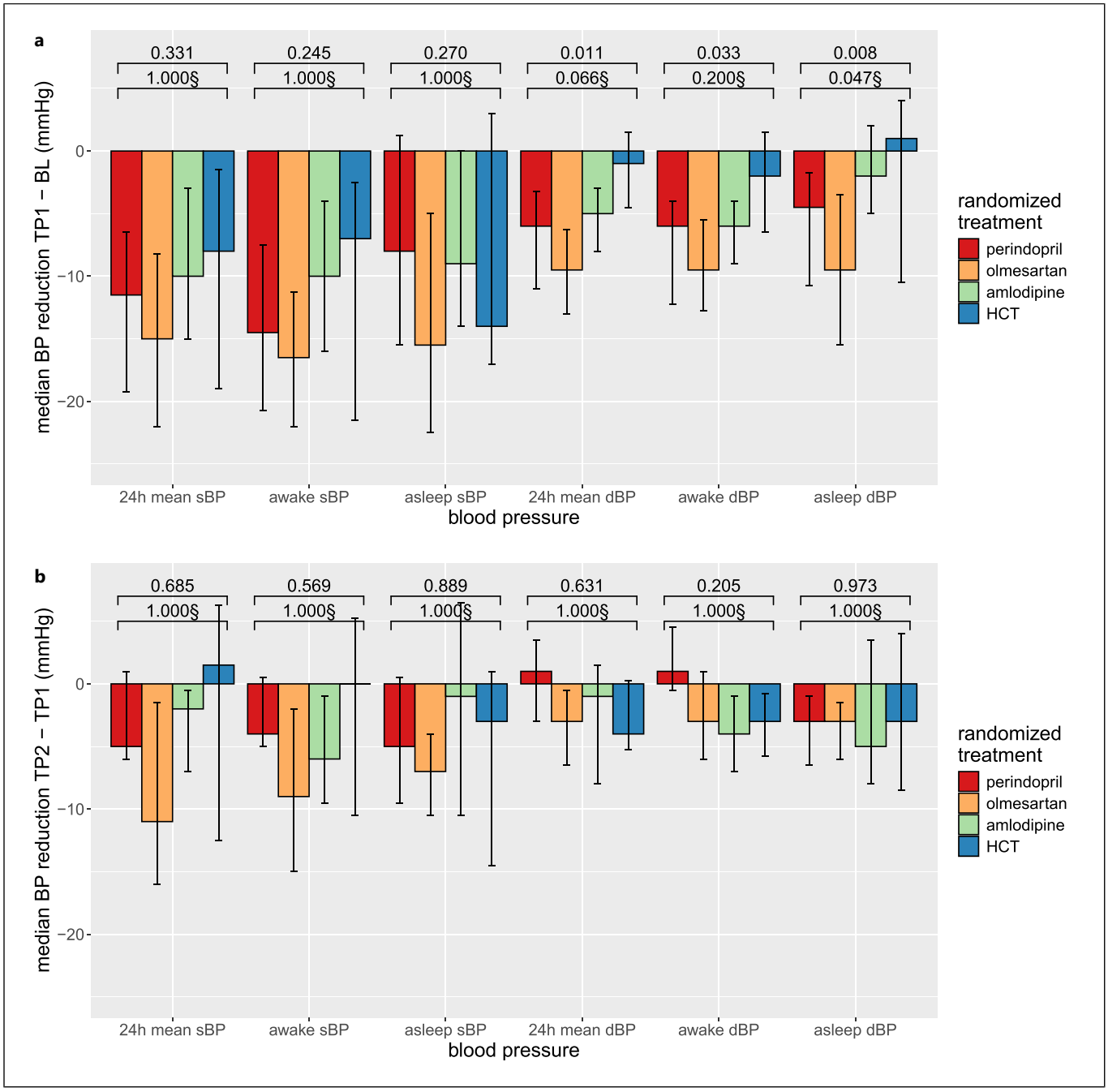


Fig. 2. Median BP reduction for each randomized treatment. BP reduction in mm Hg from baseline to TP1 (**a**) and from TP1 to TP2 (**b**) for systolic 24-h mean, awake, asleep, diastolic 24-h mean, awake, and asleep ABPM values. Upper *p* values calculated with a Kruskal-Wallis test. *p* values with § are adjusted by the Bonferroni method.

olmesartan (adjusted *p* value 0.030, online suppl. Table S4). There were no significant differences regarding the number of patients with a SBP reduction ≥5 mm Hg, and the number of patients with a systolic and diastolic BP reduction ≥10 mm Hg between the four drugs (online suppl. Tables S3, S5, S6). Patients treated with olmesartan showed a uniform reduction of both 24-h mean sBP and dBP values, whereas there were large

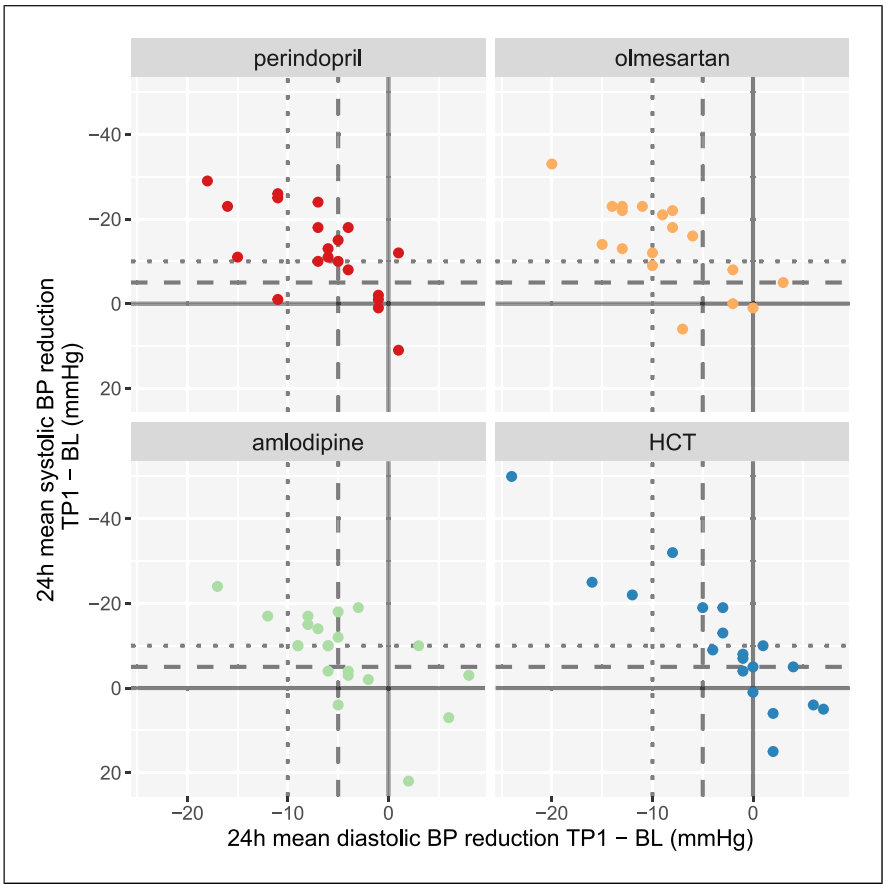


Fig. 3. Individual BP reduction per patient. BP reduction from BL to TP1 for each randomized treatment (perindopril, olmesartan, amlodipine, or hydrochlorothiazide [HCT]) for 24-h mean BP, calculated as 24-h mean BP at TP1 minus BL. The x axis depicts diastolic BP reduction, the y axis systolic BP reduction. Each dot signifies a single patient. The top left corner of each panel signifies the best BP reduction, whereas the bottom right corner of each panel signifies BP increase.

differences between the individual BP reduction in patients treated with HCT (Fig. 3). Patients treated with perindopril showed a similar distribution of individual 24-h mean sBP and dBP values to patients treated with olmesartan, and patients treated with amlodipine have a distribution of individual 24-h mean sBP and dBP values between the extremes of patients treated with olmesartan or HCT (Fig. 3). This effect is less pronounced regarding awake sBP and dBP values and more pronounced regarding asleep sBP and dBP values (online suppl. Fig. S2). 72% of patients treated with olmesartan had a BP reduction of ≥5 mm Hg for both systolic and diastolic values on 24-h mean at TP1, as did 60% of patients treated with perindopril and 53% of patients treated with amlodipine, whereas this accounted for 27% of patients treated with HCT (online suppl. Fig. S3). Regarding asleep values, 67% of patients treated with olmesartan had a BP reduction of ≥5 mm Hg, whereas this accounted for 40% of patients treated with perindopril, 34% of patients treated with amlodipine, and 32% of patients treated HCT (online suppl. Fig. S3).

Blood Pressure Control

Over all treatment groups, 32 patients (41%) reached systolic, 24 patients (31%) diastolic, and 21 patients (27%) systo-diastolic BP control after TP1. Additional 8 patients (10%) reached systolic, 6 patients (8%) diastolic, and 3 patients (4%) systo-diastolic BP control after TP2.

The proportion of patients reaching BP control after TP1 and TP2 is shown in Figure 4. The systo-diastolic BP control rates after TP1 with perindopril and olmesartan were 40% and 39%, respectively, and further results are summarized in Figure 4. In patients treated with perindopril, no additional patients and in patients treated with olmesartan 11% additional patients reached systo-diastolic BP control after TP2. Five percent of patients treated with HCT reached systo-diastolic BP control after TP1, and no additional patients after TP2. Patients without dose increase after TP1 due to clinical reasons are marked as "no dose increase after TP1" in Figure 4.

The proportion of patients in each BP category after TP1 is shown in Figure 5. The recommended optimal BP category, corresponding to an office BP of 120–129/

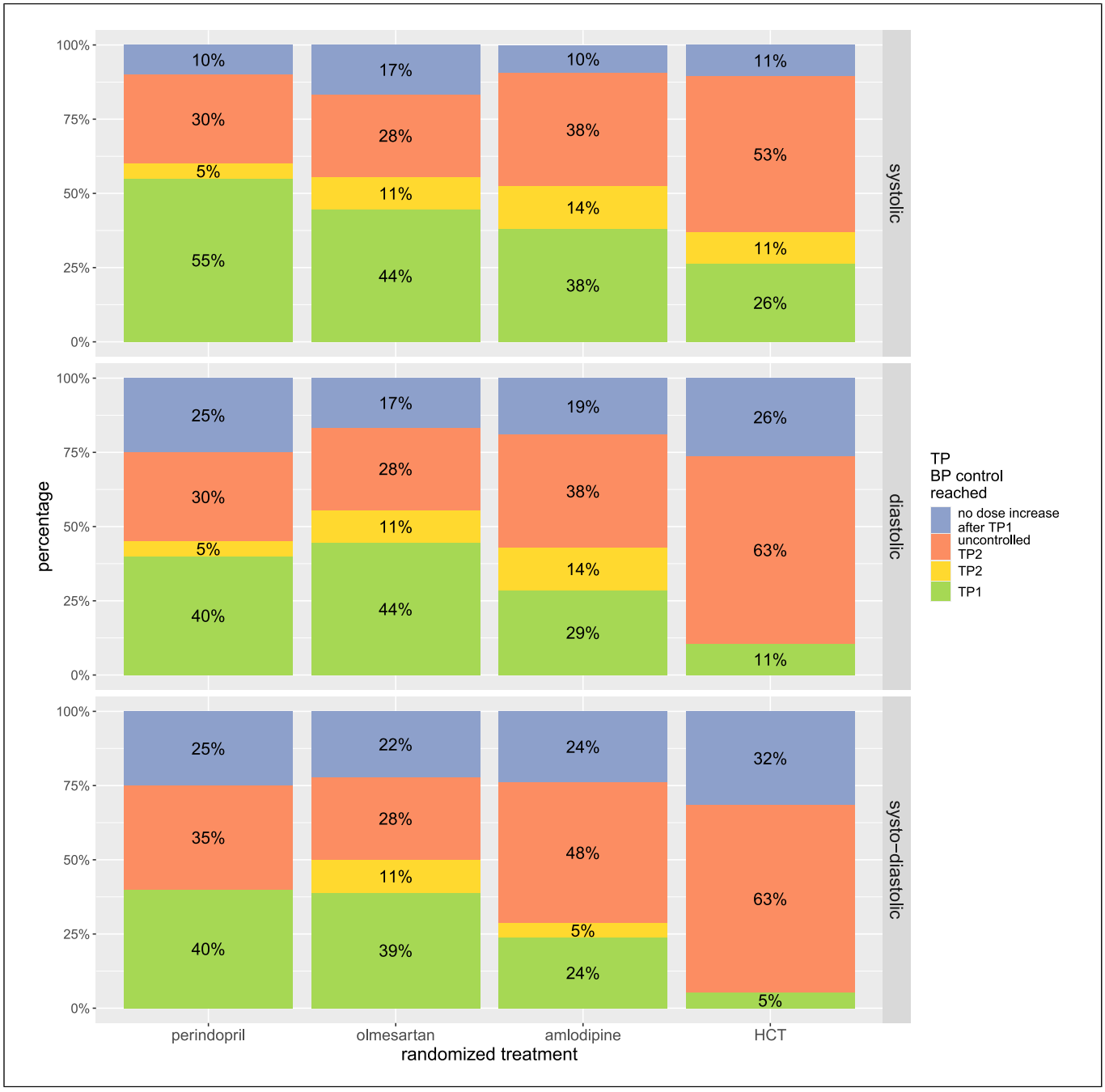


Fig. 4. BP control for each randomized treatment. Percentage of patients reaching BP control over 24 h, awake and asleep values for systolic, diastolic, and systo-diastolic values after TP1 (green), TP2 (yellow). Salmon indicates patients who did not reach BP control, blue indicates patients who were not treated to protocol, either because it was clinically decided that continuation to TP2 would be inadequate because of very low BP values or side effects, or because the patients discontinued the study during TP2.

70–79 mm Hg, was reached by 30%/25% of patients treated with perindopril, 28%/22% of patients treated with olmesartan, 14%/14% of patients treated with amlodipine, and 11%/11% of patients treated with HCT for systolic/diastolic 24-h mean values, respectively. Over all treatment groups, this goal was reached by 21%/18% for

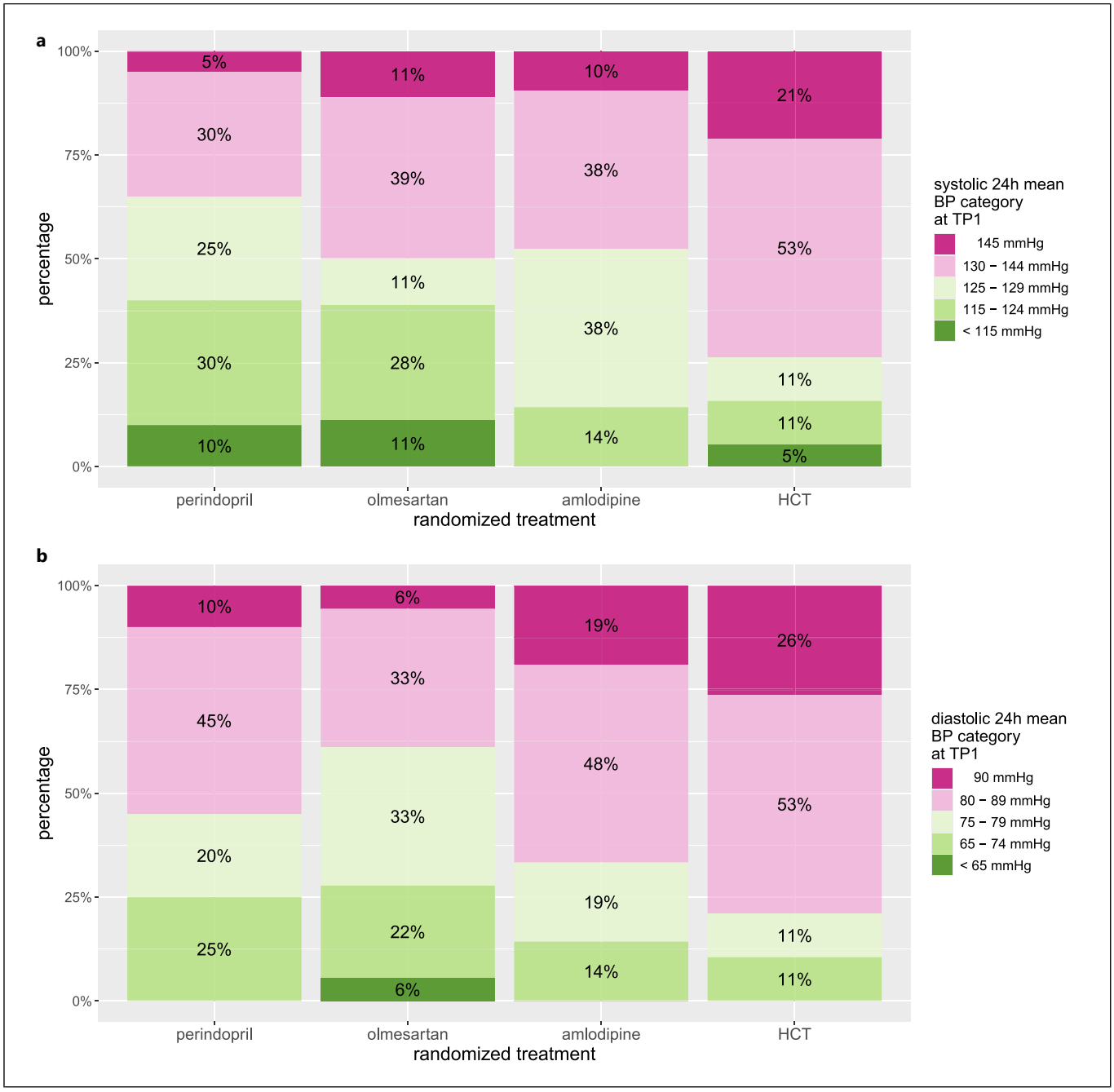
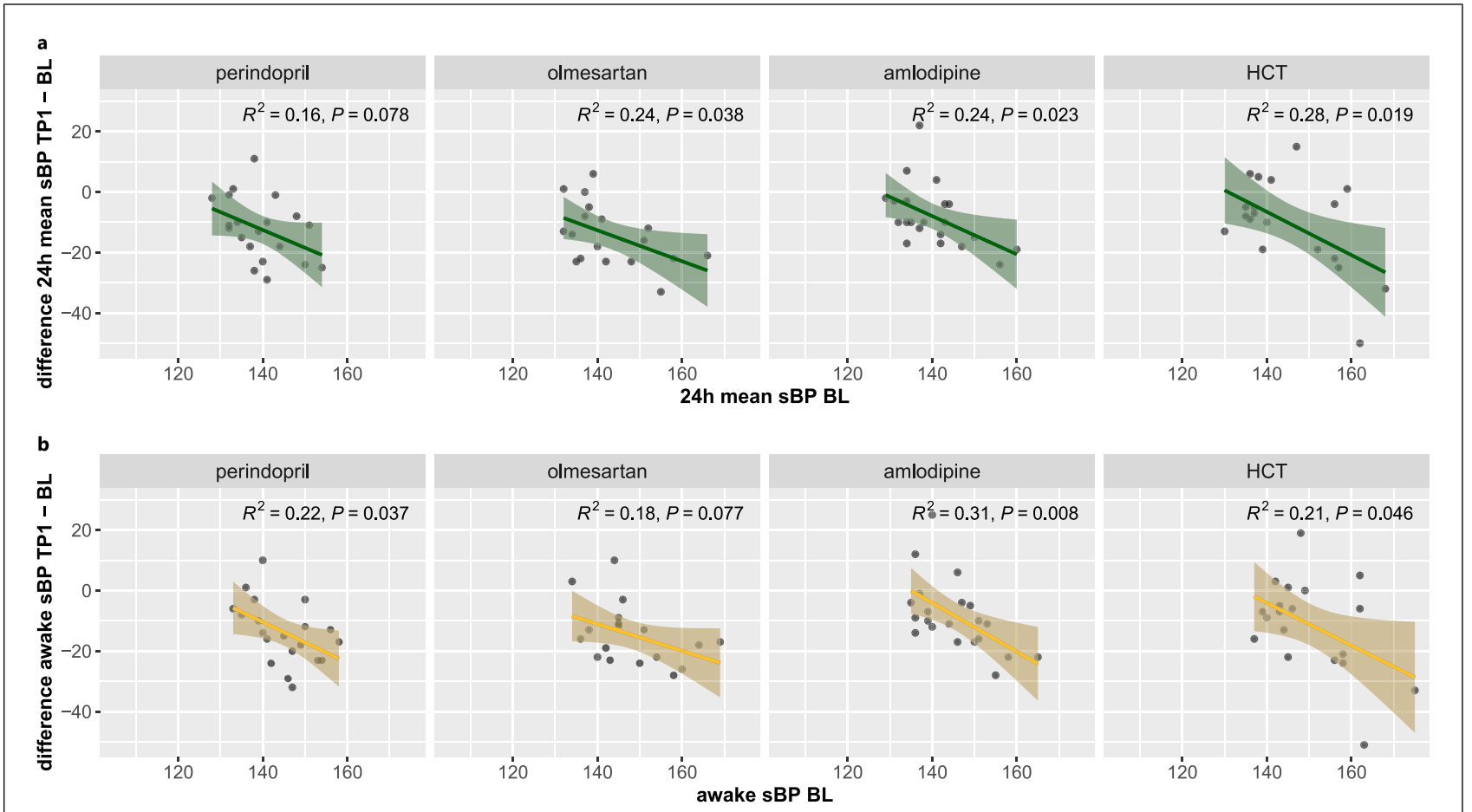


Fig. 5. BP category reached for 24-h mean BP at TP1 for each randomized treatment. Systolic and diastolic values were analyzed separately. **a** Systolic values. **b** Diastolic values. Dark magenta: ≥145/≥90 mm Hg, light pink: 130–144/80–89 mm Hg, very pale green: 125–129/75–79 mm Hg, light green: 115–124/65–74 mm Hg, and dark green: <115/<65 mm Hg.

systolic/diastolic 24-h mean values, respectively. Five/10% of patients treated with perindopril, 11%/6% of patients treated with olmesartan, 10%/19% of patients treated with amlodipine, and 21%/26% of patients treated with HCT remained in grade 2 HTN for systolic/diastolic 24-h mean values, respectively. Over all treatment groups, 12%/15% remained in grade 2 HTN for systolic/diastolic 24-h mean values, respectively.



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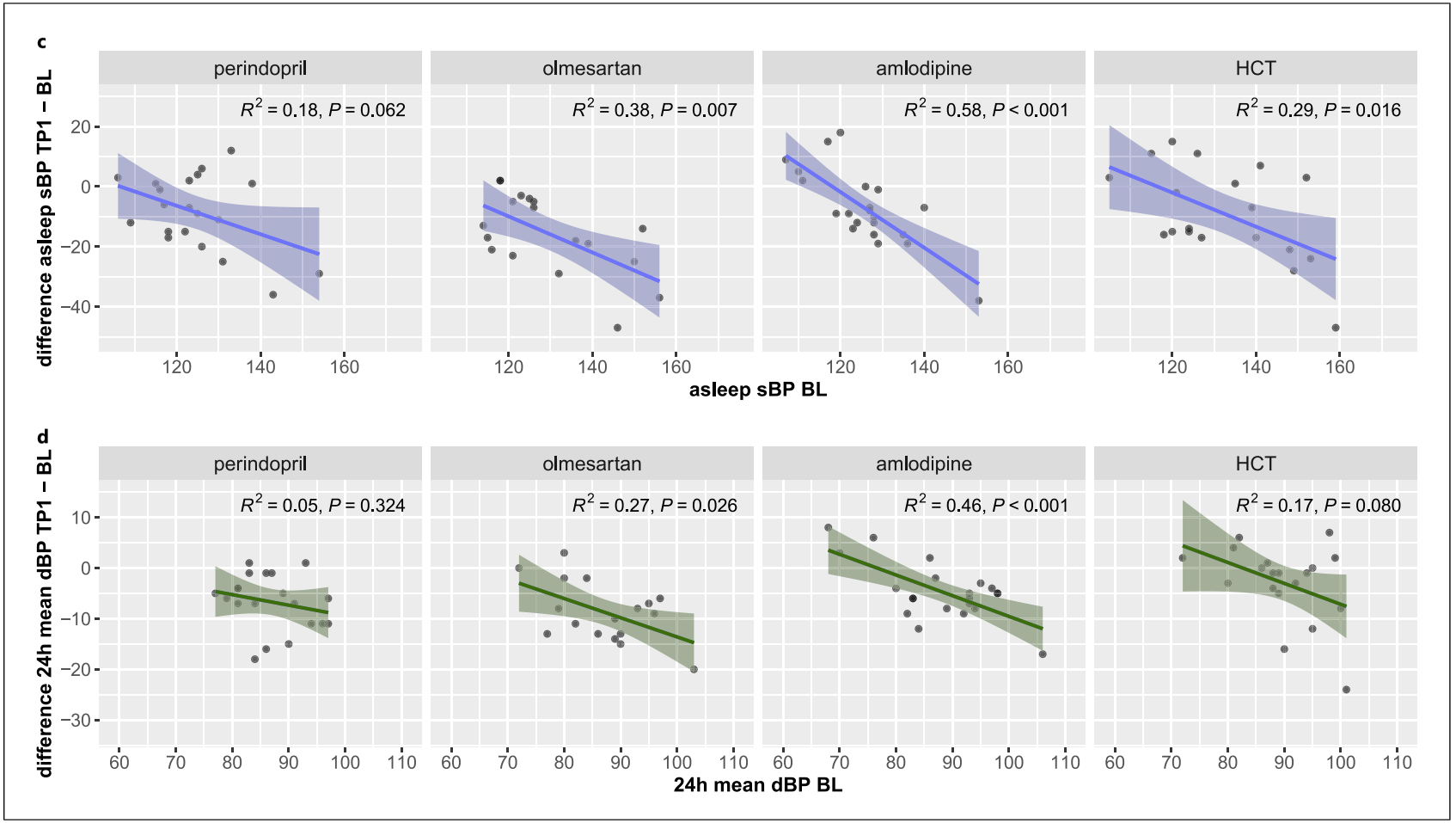

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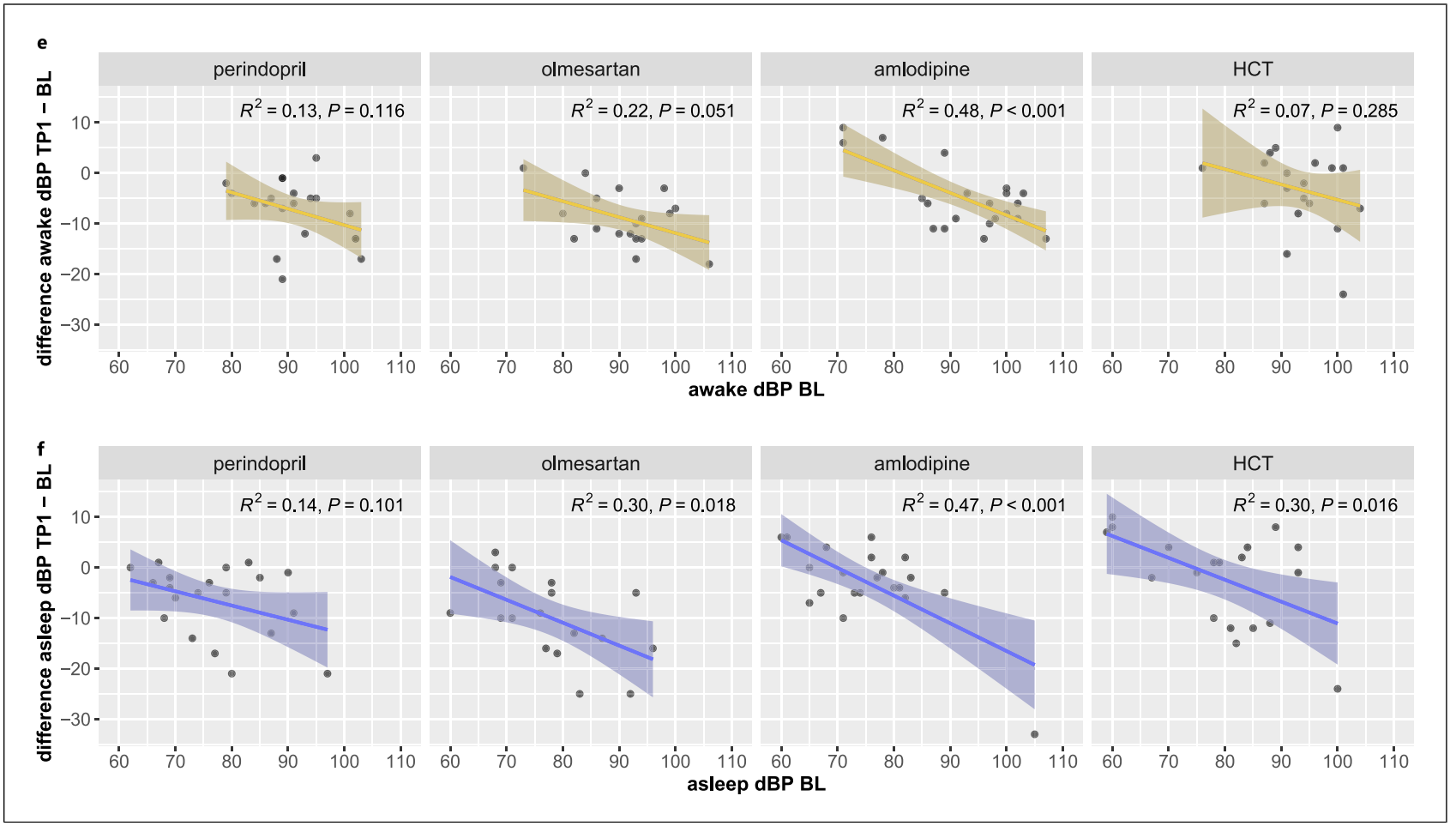

Fig. 6. Linear models predicting BP reduction from BL BP values. **a–c** Systolic values. **d–f** Diastolic values. **a**, **d** 24-h mean (green) values. **b**, **e** Awake (yellow) values. **c**, **f** Asleep values (blue). The x axis displays the BP values at BL, the y axis the BP reduction displayed as TP1 – BL. The line depicts the result of the linear model equation, the band the standard error of the equation.

Dependence of BP Reduction from Baseline BP

There is a linear relationship between the ABPM values at BL and the BP reduction between BL and TP1, particularly for amlodipine for systolic and diastolic values and HCT for systolic values (Fig. 6). This linear relationship explains <60% of the observed variation even in the best models (i.e., asleep systolic BP reduction in amlodipine: R^2 58%). Because of the low number of patients in TP2, we did not calculate prediction of BP reduction for TP2.

Correlation of BP Reduction with Baseline Characteristics

We found that female participants showed less BP reduction than men in 24-h mean dBP and awake dBP values (tau 0.500 and 0.480, and p value 0.015 and 0.020, respectively, online suppl. Fig. S4). There was no correlation between the participants' age, body mass index, or whether they had any comorbidities with the BP reduction from BL to TP1 (online suppl. Fig. S5, S6, S7).

Discussion

In this post hoc analysis of treatment-naïve patients with HTN randomized to treatment either with perindopril, olmesartan, amlodipine, or hydrochlorothiazide (HCT), we found that monotherapy with a half dose led to BP control in ABPM in only 27% of patients in total and up to 40% in those treated with inhibitors of the renin-angiotensin-aldosterone system, without significant improvement after increasing to full-dose treatment. Even in this cohort, characterized by patients with predominantly mild to moderate elevations of BP, antihypertensive monotherapy reached low BP control rates, although control of sBP was somewhat better than that observed in dBP management. Olmesartan resulted in the largest BP reduction, especially in diastolic BP values, whereas HCT was the least effective, particularly regarding diastolic values. Doubling the dosage of monotherapy in our trial numerically lowered BP, especially sBP with olmesartan, but did not improve BP control, mainly due to failing diastolic targets. The observed differences were not statistically significant, mainly due to the small sample size and the multiple comparisons.

Regarding individual response to antihypertensive treatment, we found that olmesartan led to the most uniform BP reduction over all patients, regarding 24-h mean, awake, and asleep values. Our data show that patients treated with HCT show either a strong BP reduction or none at all, particularly regarding asleep values. This large variability can be illustrated by which BP category was achieved after treatment with an intermediate dose: for example, 5% of patients treated with an intermediate dose of HCT, reached systolic BP values below the lower limit of the recommended BP target, while 21% of the patients treated with HCT remained in stage 2 HTN [4]. Though there was a linear relationship between the BP values at BL and the BP reduction between BL and TP1, the amount of this BP reduction could only predict a small part of the BP reduction observed.

Particularly, the analysis of the individual response and the number of patients reaching BP control are a strength of our study. There are several previous trials which studied the response across different antihypertensive drug classes. A trial by Dickerson et al. [20] treated patients sequentially with lisinopril, bisoprolol, HCT/triamterene, and nifedipine and then again with the best drug for the individual patient, followed by a dual combination. In this trial, 73% of participants reached the treatment target of <140/90 mm Hg in office BP; however, this number was only reached after a rotation scheme using 2 to 4 classes of antihypertensives in monotherapy [20]. Only 46% of participants reached the BP target of <135/85 mm Hg. Furthermore, it was not stated which drug class was the most effective [20]. The ADLIB trial studied a sequential treatment with amlodipine, doxazosin, lisinopril, bisoprolol, bendrofluazide, and placebo in a similar fashion to the previous trial [21]. Less than 50% of the participants had a BP below the target level on their "best" treatment, and all studied drugs were the "best drug" for at least 1 patient [21]. Another trial comparing lisinopril, candesartan, amlodipine, and HCT sequentially and in combination did not study BP goals reached but BP reduction in general [22]. However, the method applied in these trials was proven not to be feasible in clinical practice as it takes months and many visits to find the perfect drug for each patient, which was one additional reason why the ESC/ESH guidelines for the treatment of HTN replaced the stepwise approach by initial combination treatment [6].

Though there were no significant differences between the different BP-lowering drugs in our study, there was a trend of a lower efficacy of HCT particularly in comparison to RAAS blockers: similar results were found in a previous 6-week double-blind randomized trial that compared monotherapy with HCT 12.5 mg to monotherapy with candesartan 8–16 mg in 19 patients with isolated systolic HTN and a median age of 68 years. Treatment with candesartan resulted in superior BP management compared to HCT. Factorial analysis revealed that HCT in this low dosage had no significant impact on daytime systolic BP on ABPM, even when compared to a placebo [23]. However, despite HCTs apparently lower efficacy in controlling BP, a large meta-analysis that included 247,006 individuals and conducted head-to-head comparisons of the major BP-lowering classes showed

diuretics to be superior to ACEi, ARB, and CCB in preventing heart failure. RAAS blockers, including both ACEi and ARB, exhibited the same effects across all outcomes, though ACEi had some advantage and ARB some disadvantage in the risk of coronary heart disease. CCB were shown to be superior to other drug classes in preventing stroke and all-cause mortality but had disadvantages in reducing the risk of heart failure. However, with regard to most CV outcomes, all classes were equivalent when their BP-lowering effects were the same [24]. This supports the idea that the reduction of CV events is primarily due to the lowering of BP itself, rather than the specific characteristics of each drug.

Our results support that most patients, even those with mild HTN, will not achieve BP control with a single drug especially in the era of lower BP targets ranges [4]. Furthermore, our data show that BP reduction cannot simply be predicted from the BP level at BL. This means that even in patients with mild HTN, the BP reduction achieved by a single antihypertensive drug may not be enough to reach BP control; therefore, other predictors need be identified. Though we have not compared monotherapy with combination therapy, the low percentage of our participants even with relatively mild HTN with monotherapy supports the approach to initiate antihypertensive treatment directly with combination treatment [25, 26]. The basis of this recommendation is that combination treatment has the potential to overcome counter-regulatory mechanisms, such as changes in the renin-angiotensin-aldosterone system, with increasing angiotensin II equilibrium concentrations under treatment with ARB, CCB, and HCT, but not with ACE-I, which we have shown previously in this cohort [12, 27]. Additionally, our data support the approach of preferring low-dose combination treatment over high-dose monotherapy to achieve the greatest effect with the lowest risk of side effects of the respective drugs [28, 29].

When weighting efficacy against risk, the unfavorable side effect profile of thiazide diuretics has to be considered when compared to ACE inhibitors, ARBs, and CCBs, i.e., such as potentially hypokalemia, gout, new-onset diabetes mellitus, skin allergy, or elevation of creatinine level [30]. It also has to be kept in mind that thiazide diuretics tend to have the lowest adherence rates in comparison to other antihypertensive drugs due to its side effects, which may further compromise the BP lower efficiency [31].

Previous data has shown that HCT may be shorter acting, in comparison to a different thiazide-like diuretic, chlorthalidone [32]. Our data show, however, that this appears not to be the case for all patients. A possible explanation for the heterogenic BP reduction in patients treated with HCT in our study could be that patients with better adherence show a very good response to treatment, though possibly some of the patients with increasing BP values under treatment with HCT were not perfectly adhering to the study drug. Though there is a linear relationship between the BP values at BL and the BP reduction found at TP1, the amount of BP reduction cannot solely be explained by the BP value at BL. This was apparent for all drugs tested in our study, including HCT. Therefore, this effect cannot be explained by the not significantly higher BP values at BL in the HCT group.

We agree with Messerli et al. [33] that thiazides should be used reluctantly whenever other antihypertensive drugs are available, especially in the case of monotherapy. The former assumption that thiazide diuretics are more effective in the black population is also being increasingly revised [34, 35]. Nevertheless, thiazide/-like diuretics remain an essential component of antihypertensive combination treatment [29, 36].

Limitations

This is a post hoc analysis of a study which was designed to generate hypotheses such as whether a specific subgroup could profit from monotherapy, maybe with a specific drug, or if BP control with monotherapy appears unpredictable from usual clinical parameters, and to proof existing concepts. Due to the nature of the study and the limited number of participants results do not have the same statistical significance and robustness as a corresponding RCT with the primary endpoint of BP control and a prior power calculation. The study was not powered to detect differences in the BP-reducing capacities between the drug classes used in this study. There was no comparison against placebo, so there is no possibility to assess the natural course of the disease in this study. Some patients were examined using cuffless ABPM-monitors, which were considered as validated at the time of the study but are now advised against for clinical decisions by the latest HTN guidelines [4, 15]. However, follow-up ABPM was done in all patients with the same device which was used at BL. Furthermore, the participants were quite young with a median age of 49 years and results may not be directly applicable to the older population. Some patients were not treated according to protocol. Usually, these patients either had low systolic or diastolic BP values, but remained insufficiently treated on the other BP value, or they suffered from side effects, but may also include and reflect therapeutic inertia or the participant's unwillingness to increase the treatment after just 4 weeks, both of which are important reasons why BP control in general, in addition to the choice of medication, is often difficult to achieve. The decision to not continue to the next TP was done by the treating physician. There is no universal

definition to classify BP response for either systolic or diastolic BP values. Therefore, we defined as a compromise the cut-offs of 5 and 10 mm Hg for response and super response for both systolic and diastolic BP values to examine the general response.

Conclusions

In this study, we confirmed that initial monotherapy often fails to achieve BP control in a significant proportion of patients with previously untreated mild to moderate arterial HTN, with only 27% reaching minimal systo-diastolic BP control, and 21% reaching systolic and 18% diastolic optimal treatment goals with the initial dose. Only few additional patients reach BP control by doubling the dose. However, our findings uniquely demonstrate that the effectiveness of monotherapy varies significantly between drug classes, with inhibitors of the renin-angiotensin-aldosterone system – particularly olmesartan – achieving the most consistent BP reduction, while HCT showed the least efficacy, especially for diastolic BP. These findings underscore the limitations of monotherapy and support current guideline recommendations favoring combination therapy.

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Statement of Ethics

The trial followed the ethical guidelines of the Declaration of Helsinki and the applicable International Conference on Harmonization (ICH) guidelines on good clinical practice. The trial was approved by the Local Ethics Committee (Ethics Committee of northern and central Switzerland (EKNZ) 2015-081) and registered on www.ClinicalTrials.gov (NCT02449811). All patients gave written informed consent, on which they were informed that analyses would include influences of the drugs on BP changes.

Conflict of Interest Statement

A.S.V. has received personal fees from Bristol Myers Squibb, Amarin, Servier, Medtronic, Vifor, Novo Nordisk, and AstraZeneca outside the submitted work. T.B. has received fees from Servier, Sanofi Aventis, Novo Nordisk, AstraZeneca, and Daiichi Sankyo; all transferred to the research fund of the Medical Outpatient Department and Hypertension Clinic, University Hospital, and research grants by Collabree, Medtronic, and Novartis outside the submitted work. T.S. has received funding from the Roche Diagnostics outside of this work. M.B., V.V., F.K., M.M., and M.H. have no conflicts of interest to declare.

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Author Contributions

Conceptualization and methodology: A.S.V., M.H., and T.B.; software, formal analysis, and visualization: A.S.V.; validation and data curation: A.S.V., V.V., and F.K.; investigation: A.S.V., T.S., and T.B.; resources: M.M. and T.B.; writing – original draft preparation: A.S.V. and M.B.; writing – review and editing: A.S.V., M.B., and T.B.; supervision: A.S.V. and T.B.; project administration and funding acquisition: M.H. and T.B. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Data are not available due to ethical restrictions. Further inquiries can be directed to the corresponding author.

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