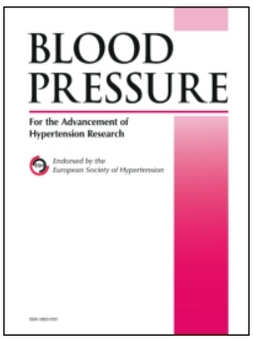

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Assessment of a strategy combining ambulatory blood pressure, adherence monitoring and a standardised triple therapy in resistant hypertension

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Assessment of a strategy combining ambulatory blood pressure, adherence monitoring and a standardised triple therapy in resistant hypertension

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ABSTRACT

Purpose: Poor adherence to drug therapy and inadequate drug regimens are two frequent factors responsible for the poor blood pressure (BP) control observed in patients with apparent resistant hypertension. We evaluated the efficacy of an antihypertensive management strategy combining a standardised therapy with three long acting drugs and electronic monitoring of drug adherence in patients with apparent resistant hypertension.

Materials and Methods: In this multicentric observational study, adult patients with residual hypertension on 24 h ambulatory BP monitoring (ABMP) despite the use of three or more antihypertensive drugs could be included. Olmesartan/amlodipine (40/10 mg, single pill fixed-dose combination) and chlorthalidone (25 mg) were prescribed for 3 months in two separated electronic pills boxes (EPB). The primary outcome was 24 h ambulatory systolic BP (SBP) control at 3 months, defined as mean SBP <130 mmHg.

Results: We enrolled 48 patients (36.0% women) of whom 35 had complete EPB data. After 3 months, 52.1% of patients had 24 h SBP <130 mmHg. 24 h SBP decreased by respectively −9.1 ± 15.5 mmHg, −22.8 ± 30.6 mmHg and −27.7 ± 16.6 mmHg from the tertile with the lowest adherence to the tertile with the highest adherence to the single pill combination ($p = 0.024$). A similar trend was observed with tertiles of adherence to chlorthalidone. Adherence superior to 90% was associated with 24 h systolic and diastolic blood pressure control in multiple logistic regression analysis (odds ratio = 14.1 (95% confidence interval 1.1–173.3, $p = 0.039$).

Conclusions: A simplified standardised antihypertensive therapy combined with electronic monitoring of adherence normalises SBP in about half of patients with apparent resistant hypertension. Such combined management strategy enables identifying patients who need complementary investigations and those who rather need a long-term support of their adherence.

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Resistant hypertension; blood pressure control; fixed-dose combination therapy; electronic pill boxes; treatment adherence

Introduction

Hypertension is defined as resistant to therapy when the prescribed drug treatment fails to control blood pressure (BP) and to achieve recommended targets, and the inadequate BP control is confirmed by out-of-office BP monitoring in patients whose adherence to therapy has been confirmed [1]. This definition implies that 3 antihypertensive drugs are prescribed at maximally tolerated doses with one of them being a diuretic. In recent years, additional definitions have appeared in the literature [2]. They include the concept of refractory hypertension, when BP remains uncontrolled with the use of ≥5 antihypertensive agents of different classes, including a long-acting thiazide-like diuretic and spironolactone, or controlled resistant hypertension, when BP falls below targets on ≥4 antihypertensive medications at maximal or maximally tolerated doses [2]. Frequently, however, uncontrolled hypertension is considered as 'apparent' rather than true resistant hypertension because BP

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has not been measured outside the office, drug adherence has not been assessed and other factors of pseudo-resistance have not been excluded [3].

The prevalence of apparent or true resistant hypertension varies depending on the definition used and the context in which prevalence was estimated (e.g. from referral populations or clinical trial participants). In the 2003–2008 National Health and Nutrition Examination Survey (NHANES), 12.8% of the drug-treated hypertensive patients fulfilled the criteria of apparent resistant or refractory hypertension [4]. In a pooled analysis of multiple studies, the prevalence of resistant hypertension was 14.8% in treated hypertensive patients and 12.5% in all hypertensive patients but true resistance probably represented only half of these percentages [3]. In a recent analysis of US data using the newer 2017 American College of Cardiology/American Heart Association (ACC/AHA) hypertension guidelines, the prevalence of apparent resistant hypertension was 19.7%. [5] However, after applying a strict definition and having excluded all causes of pseudo-resistance, the true prevalence of resistant hypertension was rather lower than 10% [1]. The prevalence may be higher in patients with chronic kidney diseases [6] or patients addressed to tertiary reference centres because their BP remains uncontrolled despite treatment [7,8].

With the development of device-related antihypertensive therapies, which initially focussed on treating patients with resistant hypertension, the screening of these patients has revealed that pseudo-resistance is common and due either to white-coat hypertension [9] or to a poor adherence to drug therapies [10]. Moreover, inadequate therapies are another frequent factor affecting BP control. Indeed, across European Hypertension Excellence Centres, inadequate treatment was a non-eligibility criterion in 46.9% of the cases referred for renal denervation [11]. Hence, several recommendations for the management of patients with apparent resistant hypertension have been published emphasising the need of an objective assessment of treatment adherence, the use of appropriate BP measurement techniques to exclude pseudo-resistance and the prescription of spironolactone as adjunctive therapy on top of maximally tolerated conventional triple therapy [1,12–14].

The objective of our study was to assess prospectively the efficacy of a new management strategy combining the use of ambulatory BP monitoring (ABPM), electronic monitoring of drug adherence and prescription of a standardised antihypertensive therapy using 3 long-acting antihypertensive drugs, including a single pill combination, on the rate of ambulatory BP control in patients referred to tertiary care centres because of resistant hypertension.

Patients and methods

This was a multi-centre observational prospective study conducted in three Swiss Hypertension Excellence centres (Geneva, Lausanne and Luzern) between April 2011 and May 2017 (NCT01083017). The trial protocol was approved by the institutional review board in each site and conducted in accordance with Good Clinical Practice. All patients included in the study signed a written-informed consent.

We included adult patients referred for apparent resistant hypertension on three or more antihypertensive drugs and residual hypertension on 24 h ABPM defined by mean 24 h BP $>$ 130/80 mmHg. Patients with estimated glomerular filtration rate (eGFR) lower than 30 ml/min/1.73 m2, with a clear indication for blockers of the mineralocorticoid receptor (heart failure with an ejection fraction $<$45%) or with hyperkalemia ($>$5 mmol/L) were excluded from the study.

After inclusion, all patients received a once a day single pill combination of olmesartan 40 mg and amlodipine 10 mg together with 25 mg chlorthalidone for 3 months. Medications were provided in two separated electronic pill boxes Medical Event Monitoring System, MEMS, AARDEX, Ltd, Zug, Switzerland). No washout period was included in the protocol. As blood pressure endpoints were measured after 3 months, a carryover effect of antihypertensive drugs prescribed before the standardised treatment seemed extremely unlikely. The protocol of the management algorithm is shown in Supplemental Figure 1. The EPB records the date and time of each opening of the pillbox as described previously [15]. The follow up included visits at 6 and 12 weeks. At 3 months, we analysed the EPB data to assess the dosing history and a second ABPM was performed to evaluate the out-of-office BP control. ABPM devices were programmed to take BP every 20 min during the day and 30 min during the night. BP cuff was adapted to arm circumferences. Day and night BP was defined according to sleep and wake-up time reported by patients in their diary. ABPM was considered of satisfactory quality if at least 20 measures were available during the day and at least 7 measures during the night [16].

The primary endpoint was the control of ambulatory systolic BP (SBP) at 3 months defined as mean

24 h SBP <130 mmHg. Secondary endpoints included the control of daytime (<135 mmHg), nighttime (<120 mmHg) SBP and 24 h (<80 mmHg), daytime (<85 mmHg), nighttime (<70 mmHg) DBP at 3 months. It also included the differences in 24 h ambulatory SBP and DBP across levels of adherence to the prescribed drugs.

Adherence data were analysed using so-called 'taking adherence', which is defined as the proportion of prescribed drugs taken during the time window and calculated as the number of openings/number of prescribed doses ×100. It takes into account both the average dose received over a given period of time and the total dose received over that period.

Statistical analysis

The data analysis was performed on the group of patients who accepted to participate in the study and who completed the ABPM measurements with sufficient quality (ABPM set) and in the subset of patients for whom we had a complete data set for both the adherence monitoring and ABPM (ABPM/EPB set). Data are presented as mean ± standard deviation (SD) or interquartile range (IQR) whenever appropriate. We used paired t-test, Wilcoxon matched-pairs signed-rank test, Wilcoxon rank-sum test, chi-squared to compare groups or within groups changes. In unadjusted analyses, we used a nonparametric test for trend across categories of BMI (nptrend function in Stata developed by Cuzick, which is an extension of the Wilcoxon rank-sum test). Logistic regression was used to analyse the effect of potential factors such as adherence category, level of blood pressure, age, sex and estimated filtration rate (independent variables) on the control of 24 h BP (dependent variable). Analyses were performed using STATA 14.0 (Stata Corp, College Station, USA). A two-side $p < 0.05$ was considered as statistically significant.

Results

The study flowchart is shown in Supplemental Figure 2. Out of 75 potential participants, 5 did not wish to switch their treatment. In addition, 22 patients were excluded because they had incomplete 24 h ABPM or ABPM of insufficient quality leaving 48 patients with complete ABPM data (ABPM set). In addition, thirteen patients (incomplete EPB set) were excluded from the adherence analysis because they refused the electronic monitoring of adherence. Thus, the second set of patients with complete ABPM and EPB data (EPB set) contained 35 patients.

Table 1 displays the baseline characteristics of the participants within the 3 data sets: the ABPM ($n = 48$), the EPB set ($n = 35$) and the incomplete EPB set ($N = 13$). No demographic differences were observed between the EPB and the incomplete EPB set.

Effect on ambulatory BP and on hypertension control at 3 months

In the ABPM set, baseline 24 h ambulatory SBP and DBP were 150 ± 21 mmHg and 90 ± 17 mmHg respectively (Supplemental Table 1). At 3 months, mean 24 h SBP decreased to 131 ± 17 mmHg ($p < 0.001$) and DBP to 78 ± 11 mmHg ($p < 0.001$). In this set of patients, 39.6% of them had a controlled 24-h ambulatory BP (both SBP and DBP) at 3 months. Daytime SBP and DBP decreased from 155/93 ± 21/17 mmHg to 134/81 ± 17/12 mmHg (both $p < 0.01$); nighttime SBP and DPB decreased from 139/82 ± 24/17 mmHg to 121/69 ± 20/11 mmHg (both $p < 0.01$). The percentage of patients with a controlled 24 h, daytime and

Table 1. Baseline characteristics of patients in the two data sets.

	ABPM set	EPB set	Incomplete EPB set	*p*
N	48	35	13	
Sex (male, %)	64.6	63.9	61.5	0.78
Age (years) (range)	56.5 ± 11.5	56.1 ± 11.8	57.8 ± 11.1	0.68
Body mass index (kg/m2)	31.0 ± 4.6	31.1 ± 5.1	30.7 ± 3.4	0.83
Serum creatinine (µmol/l)	88.9 ± 26.9	86.9 ± 23.9	94.1 ± 34.1	0.41
Plasma sodium (mmol/l)	140 ± 2	139 ± 2	141 ± 3	0.07
Plasma potassium (mmol/l)	3.8 ± 0.4	3.9 ± 0.4	3.7 ± 0.4	0.15
Ethnicity (Caucasian)	77.1	77.1	76.9	0.81
Cardiovascular history (%)	12.5	8.6	23.1	0.17
Diabetes mellitus (%)	59.6	57.1	66.7	0.56
Current smoking (%)	45.7	37.1	61.5	0.13
Office SBP (mmHg)	163 ± 21	164 ± 21	160 ± 21	0.47
Office DBP (mmHg)	93 ± 18	93 ± 18	93 ± 18	0.93
Number of BP lowering drugs	3.7 ± 0.9	3.7 ± 0.8	3.8 ± 1.0	0.84

Data are means ± standard deviations or proportion expressed in percentage. ABPM: ambulatory blood pressure monitoring, EPB: electronic pill box, SBP: systolic blood pressure, DBP: diastolic blood pressure. The EBP set was compared to the incomplete EPB set.

Table 2. Percentage of patients with a controlled BP control at 3 months, using various parameters of ambulatory BP monitoring in the two set of patients.

	ABPM set ($n = 48$)	EPB set ($n = 35$)
SBP and DBP controlled		
24h	39.6%	37.1%
SBP controlled		
Day	54.1 %	51.4 %
Night	47.9 %	51.4 %
24h	52.1 %	51.4 %
DBP controlled		
Day	56.3 %	60.0 %
Night	41.7 %	45.7 %
24h	60.4 %	60.0 %

ABPM: ambulatory blood pressure monitoring. EPB: electronic pill box. Criteria of controlled BP are: <135/85 mmHg for average daytime systolic and diastolic BP, <120/70 mmHg for average nighttime systolic and diastolic BP, and <130/80 mmHg for average 24 h BP.

nighttime systolic and diastolic BP is presented in Table 2.

In the ABPM/EPB group ($n = 35$), mean 24 h ambulatory SBP and DBP decreased from 148/89 ± 19/16 mmHg to 129/77 ± 17/11 mmHg (both $p < 0.001$). As shown in Table 2, 51.4% of patients had a controlled 24 h daytime SBP, 60.0% had a controlled daytime DBP and 37.1% had both the systolic and diastolic 24 h BP at target (<130/80 mmHg) after 3 months. At baseline daytime SBP and DBPs were 153 ± 20 mmHg and 92 ± 17 mmHg respectively and these values decreased to 132 ± 16 mmHg for daytime SBP ($p < 0.001$) and to 81.5 ± 11 mmHg ($p < 0.0$ 1) for daytime DBP. Nighttime SBP decreased by 18 ± 28 mmHg ($p < 0.001$) and nighttime DBP by 13 ± 17 mmHg ($p < 0.001$). Figure 1(A) shows the changes in ambulatory systolic, diastolic and 24 h BP at 3 months for this subset of patients. There was no difference between men and women in terms of frequency of controlled BP. In well-controlled patients at 3 months, systolic daytime ambulatory BP was 119 ± 9 mmHg in men and 121 ± 6 mmHg in women whereas in uncontrolled patients SBP values were 143 ± 9 mmHg and 152 ± 13 mmHg respectively for men and women.

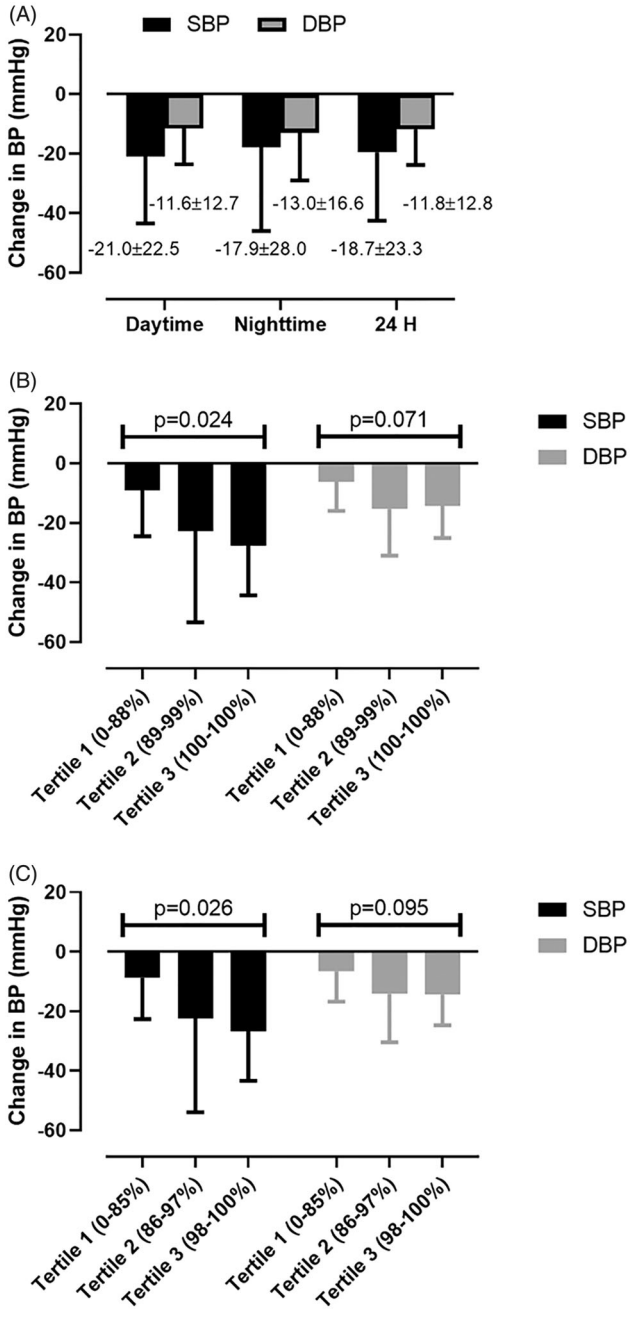

Figure 1. Change in ambulatory systolic and diastolic blood pressure after 3 months. (A) Overall change in daytime, nighttime and 24 h ambulatory blood pressure; (B) changes in blood pressure according to tertile of adherence to olmesartan/amlodipine combination and (C) changes in blood pressure according to tertile of adherence to chlorthalidone.

Medication adherence and blood pressure control

During the 3 months of monitoring, the median taking adherence was 91% (interquartile range (IQR): 83–100%) for the olmesartan/amlodipine fixed dose combination and 91% (IQR: 82–100%) for chlorthalidone. Table 3 shows the median adherence for the fixed dose combination of olmesartan/amlodipine and for chlorthalidone in patients according to whether daytime SBP was controlled or uncontrolled. The adherence to both pills tended to be better in patients with a controlled BP, yet the difference was not statistically different.

As tertiles of adherence to the olmesartan/amlodipine combination or to chlorthalidone increased, the decreases in SBP were more marked (Figure 1(B,C)). A similar trend but not significant was observed with diastolic BP. A marked decrease in BP was observed

essentially in patients with a 3-month adherence ≥ 90% compared to those with an adherence < 90%. Indeed, in patients with an adherence ≥ 90%, a statistically significant reduction of night ambulatory SBP (−25 ± 21 mmHg vs −7 ± 21 mmHg, $p < 0.05$) was observed. An adherence ≥ 90% was associated with an odds ratio of 14.1 (95% confidence interval 1.1–173.3, $p = 0.039$) to have both SBP and DBP controlled after 3 month in multiple logistic regression analysis.

Figure 2 shows the relation between daytime ambulatory systolic BP and drug adherence above or below 90%. As expected BP control was more frequent in patients with an adherence ≥ 90% and conversely uncontrolled BP was more common among patients with an adherence < 90%. Interestingly, however, 20% of patients with an uncontrolled BP had an adherence ≥ 90% suggesting a true resistance to therapy and 17% of treated patients had a controlled systolic BP despite an adherence < 90% suggesting over-treatment.

At last, according to our initial protocol of investigation (Supplemental Figure 1) 51% of the entire set of patients could be sent back to their general practitioners with a 24 h ambulatory BP <130/80 mmHg. Therefore, they were not considered as having true resistant hypertension anymore.

Discussion

In the last decade, the interest in the management of resistant hypertension has increased substantially. This has led to the publication of many recommendations dealing with the investigation and treatment of patients with resistant hypertension [1,3,10,12,17–21]. All investigation algorithms recommend to initially exclude a pseudo-resistance using out of office BP measurements [21] and an assessment of medication adherence. After these initial steps, the treatment scheme is based on the use of a blocker of the renin-angiotensin system, a calcium channel blocker and a diuretic as first steps with the addition of spironolactone as 4th drug [1,22].

In the present study, we have assessed the efficacy of a strategy combining the use of ABPM, electronic monitoring of adherence and a standard triple therapy including a single pill combination in patients with resistant hypertension. With our approach mean 24 h ambulatory systolic and diastolic BP decreased respectively by −19.6 ± 11.0 mmHg and −11.8 ± 12.8 mmHg and about 40% of patients had a 24 h ambulatory BP <130/80 mmHg at the end of the study. As expected, BP controlled was better among patients with a good drug adherence, the cut-off adherence for having a significant BP reduction being at ≥90%. However, the analysis based on BP control

Table 3. Levels of adherence to chlorthalidone and the olmesartan/amlodipine combination according to controlled or uncontrolled daytime SBP.

Adherence in %	All ($n = 35$)	Controlled daytime SBP($n = 18$)	Uncontrolled daytime SBP ($n = 17$)	p Value
Chlorthalidone	91.0 (82–100)	94.9 (85.0–100)	89.0 (70.0–97.7)	0.187
Olmesartan/amlodipine	91.0 (83–100)	97.0 (89.0–100)	89.0 (70.0–97.6)	0.08

Data are median and interquartile range. SBP: systolic blood pressure.

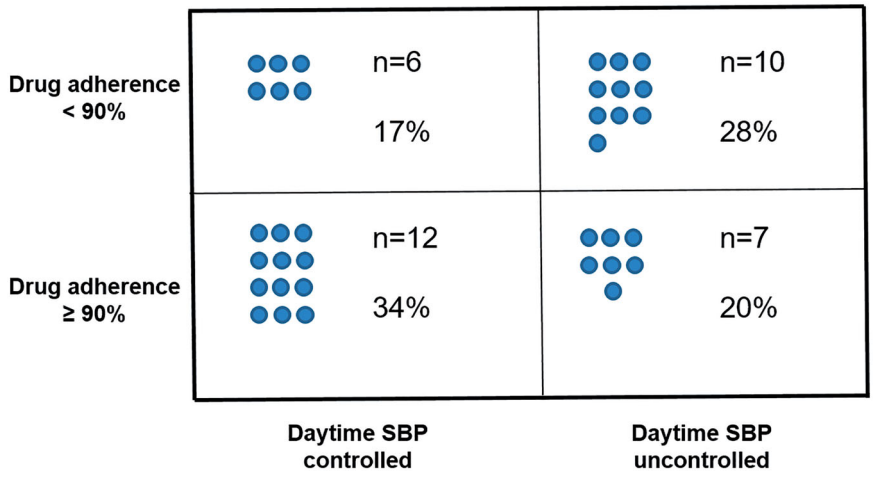

Figure 2. Distribution of patients according to controlled/uncontrolled daytime systolic blood pressure (SBP) and adherence over or under 90%.

and drug adherence revealed 20% of patients with an uncontrolled BP despite a good adherence and 17% of patients with a good control of BP but a low adherence.

Measurement of out-of-office BP, preferably using ambulatory BP monitoring, is the first investigation to perform in all patients with apparent resistant hypertension according to all recommendations [21]. Indeed, up to 30% of patients with apparent resistant hypertension may have a normal out-of-office BP [11,23,24]. In addition, ABPM enables not only to exclude pseudo-resistance but also to diagnose masked uncontrolled hypertension [21]. In the present study, ABPM was used as an inclusion criterion to enrol patients and also as an outcome. In our patients, 24 h ambulatory BP decreased by almost 20 mmHg systolic and 12 mmHg diastolic: those numbers are comparable to those reported by Gupta et al. using another management strategy [25]. More importantly, with our approach 40% were perfectly controlled at 3 months based on ABPM. There are not many comparative data in interventional studies. In the PATHWAY-2 study, the addition of a placebo on the triple-therapy background in patients with true resistant hypertension resulted in the control of 24.4% of patients whereas adding spironolactone controlled 57.8% and doxazosin 41.5% of patients [22]. Using a similar protocol but without a standard triple therapy (patients were maintained on their prescribed therapy), we reported previously that one third of patients had normalised their ambulatory BP following the 2 months monitoring [15]. These results would suggest that our combined approach is very effective in the initial management of resistant hypertension. However, due to the observational design of our study we cannot highlight, which of the factors between the standardised therapy, the electronic monitoring of drug intake or a possible Hawthorne effect had the most impact on blood pressure reduction.

Today, poor adherence to prescribed antihypertensive drugs is recognised as a major issue, which may have an important impact on BP control and cardiovascular outcomes in hypertension [26]. The prevalence of partial or complete non-adherence to drug medication is particularly high in resistant hypertension. Indeed, several retrospective and prospective studies have reported percentages of poor adherence ranging between 3 and 66% (with a mean of 33–42%) in resistant hypertension [10,27–29]. This large variability is partly explained by the different methods of adherence assessment and the clinical context. In our study, the adherence appeared to be good with a median of 91% over three months. Yet, we found that the cut-off level of adherence to obtain a significant reduction of BP in patients with resistant hypertension is >90% rather than >80%. This is in agreement with the results of a previous analysis of patients with uncontrolled hypertension, in which we found that a cut-off of 92% was necessary to have a well-controlled BP [30]. Once again, these data challenge the usual definition of adherence in terms of percentage, as discussed previously [31]. Thus, according to the 90% threshold, 45% of our patients who completed the 3-month MEMS® monitoring had a poor adherence. Nevertheless, this figure may well be underestimated as one knows that measuring drug adherence per se improves the adherence and the quality of the BP control [15,25,32].

Recommendations on the management of resistant hypertension insist on obtaining objective data on drug adherence whenever possible. In the present study, we used the Medication Events Monitoring system (MEMS®) to measure adherence. This system is largely used in clinical trials and provides the dosing history over a given time period recording the time and date of each box opening. Although it does not certify that the drug has been ingested, any non-opening of the pill box is a valid indication that the drug was not taken. Today, most centres use the measurement of antihypertensive drug levels in urines. This method guarantees that the drug has been ingested but it provides only a punctual information that may be affected by the white coat adherence. In addition, drug measurements do not provide any information on the dosing history and the percentage of pills taken during a time interval. Yet, with both methods, the most reliable information comes from the absence of drug measurable in the urine or the absence of pill box opening. Our data are in strong agreement with the results published so far with the detection of antihypertensive medications in body fluids using liquid chromatography-tandem mass spectrometry [10,33,34]. This latter method is probably easier to implement in clinical practice. In our study, 13 patients (17.8%) refused to use the MEMS system to monitor their adherence. This happens frequently in patients already using a pill organiser. However, we also noticed that the refusal was much more frequent in one of the participating centre, suggesting that introducing the electronic monitoring system needs a teaching of physicians on how to use the system and have it accepted by patients.

The original component of our assessment strategy is the use of standard triple therapy based on a single

pill combination of a calcium channel blocker and an angiotensin receptor blocker, and a thiazide-like diuretic. The three drugs used in our protocol had a very long half-life (olmesartan, amlodipine and chlorthalidone) limiting the clinical impact of missed doses [35,36]. The choice of chlorthalidone has been based on recent analyses suggesting the superiority of chlorthalidone over hydrochlorothiazide in lowering BP and preventing cardiovascular events [37,38]. This approach differs from most previously published strategies, in which the initially prescribed drugs are maintained and monitored. However, it follows current treatment guidelines suggesting to simplify the therapeutic regimen in all patients [1] and avoid dealing with under-dosed therapies, another frequent observation in patients with resistant hypertension [2]. In our hands, using a standard triple therapy, which has been reported to control BP in almost 80% of hypertensive patients [39], resulted in a slight increase in the percentage of patients achieving BP targets without noticeable side effects. Only 6.6% of patients refused to change their drug therapy.

The last interesting observation made in our study is illustrated in Figure 2. As expected, among patients with uncontrolled hypertension, some had good adherence and some other a poor adherence. In the former case, patients are certainly truly resistant and deserve additional clinical investigations to exclude secondary forms of hypertension. In the non-adherent group, health care providers should focus their action on identifying barriers to adequate adherence and thus possibly increase adherence. Another puzzling group was that of patients with a low adherence but still a well-controlled BP. These patients may receive several drugs that they don't take adequately e.g. half of the first drug and intermittent use of a diuretic. In those cases, the pertinence of the prescribed regimen should probably be reassessed.

Our study has some limits. The first is the absence of a control group following a standard protocol. However, such a study was done by our group in 2001 without standardisation of the triple therapy as discussed above [15]. The second is the loss of several patients because of incomplete ABPM or refusal of the MEMS system, which reduced the sample size of the study, thus limiting the strength of our observation. In this respect a similar protocol could be evaluated using home BP monitoring and/or the determination of drugs in the urine at various time points during the monitoring. A comparison of two assessments of adherence (electronic monitoring vs determination of drug levels in urines) or the combination of both would be of interest.

In conclusion, our study shows that a simplified and standardised antihypertensive therapy combined with a 3-month electronic monitoring of adherence and an assessment of BP control using ABPM normalises SBP in about 50% of patients with apparent resistant hypertension. The level of adherence has a major impact on the treatment-induced reduction of BP. Our results confirm that in order to reach the target 24 h ambulatory BP, patients with resistant hypertension need an adherence $> 90\%$. Combining ABPM and an objective measurement of adherence enables physicians to recognise those patients who need additional investigations or rather a program to support long-term medication adherence.

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Disclosure statement

EGB has received speaker's honoraria from Daiichi-Sankyo (olmesartan and olmesartan + hydrochlorothiazide). MB has received consulting and speaker fees from Menarini AG, Switzerland.

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