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ORIGINAL ARTICLE

Blood pressure telemonitoring is useful to achieve blood pressure control in inadequately treated patients with arterial hypertension

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Failing to reach blood pressure (BP) goals is one of the main problems in hypertension management. Especially in high-risk patients, intensive monitoring including frequently office visits or new techniques to monitor home BP is required. A total of 60 patients with uncontrolled hypertension were included and randomized into a group with telemetric BP monitoring (TBPM) ($n=30$) and a control group receiving standard care ($n=30$). During the 3-month study period, patients received in addition to their antihypertensive pre-treatment up to 2×300 mg irbesartan to achieve the required target BP. All patients were instructed to measure their BP once daily in the morning. In the TBPM group automatic alerts were generated by the central database server using pre-defined algorithms and patients were subsequently contacted by the physician. At baseline mean 24-h ambulant BP monitoring (ABPM) was $142.5\pm11.1/82.1\pm9.9$ mm Hg in the TBPM group and $141.4\pm12.6/82.1\pm6.5$ mm Hg in the standard care group. During treatment mean systolic BP showed a more intensive decrease in the TBPM vs control group (-17.0 ± 11.1 mm Hg vs -9.8 ± 13.7 mm Hg; $P=0.041$). Patients in the TBPM group had a more pronounced night dipping and a higher reduction of mean pulse pressure than controls (-8.1 ± 5.9 mm Hg vs -2.8 ± 7.4 mm Hg, $P=0.004$). After 3 months, TBPM-treated patients were given a higher mean daily dose of irbesartan (375 ± 185 mg vs 222 ± 147 mg in controls; $P=<0.001$). We demonstrated that with TBPM a more effective and faster titration of the antihypertensive agent is possible. The alarm criteria chosen were useful to improve BP control.
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Keywords: telemedicine; telemonitoring; home blood pressure; antihypertensive agents; irbesartan; treatment goals

Introduction

Arterial hypertension is one of the most widespread diseases with a prevalence of 25% in industrial nations, 50% in people over 60 years and 75% in persons suffering from obesity[1,2] and it is the main risk factor for death.[3]

Far less than half of the diagnosed blood pressure (BP) patients are treated adequately and reach target BP values, irrespective of the kind of antihypertensives used.[4] Despite the clinical burden and socio-economic costs of hypertension and its sequels the quality of BP control has remained static for the last 10 years.[5] Several factors have been attributed to be responsible for this problem:[6] (1) usage of a suboptimal dose of an antihypertensive drug;[7] (2) inadequate or insufficient combination therapy; and (3) non-adherence/non-compliance of the patient with the prescribed antihypertensive drugs.

In clinical studies and in the general practice often three to four antihypertensives are required to reach the target values recommended by the ESH/ESC guidelines.[6] Distinct BP target values for ambulant BP monitoring (ABPM) and home BP measurements (HBPM)[8] are recommended in order to prevent end organ damage.[9]

At the beginning of treatment with a new antihypertensive drug, up to two consultations a week are suggested. Even so, this would be often ideal two major limitations exist: (1) lack of time in a physician's daily routine; (2) limited financial resources to reimburse additional physician visits.[10]

To direct changes of BP medication only by ABPM results is too cumbersome for the patient and the treating physician. It is also too imprecise and not

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sufficiently reliable,[11] so that recent guidelines claim the use of both HBPM and ABPM.[8]

A recommended method to depict the real BP characteristics at the beginning of the therapy is HBPM including a patients' BP record book. Yet, there are two weak points concerning patient documentation: Incomplete and incorrect documentation.[12,13] This aspect is commonly found in patients with insufficiently controlled hypertension.[14] Therefore, it is no surprise that only approximately half of the physicians have confidence in the data of HBPM and take them into account in there decision making process.[15] telemetric BP monitoring (TBPM) should be regarded as a further development in self-measuring HBPM. The literature considers TBPM as a promising method.[16,17] Yet, alarm algorithms or a consistent therapy strategy have not been worked out.

The aim of this study was to examine the effect of TBPM and the TBPM-derived therapeutic action on the quality of BP control in a defined short-time period of 3 months.

Methods

Study design and population

A total of 60 patients with inadequately treated arterial hypertension in a 24-h ABPM reading were randomly assigned into a standard care group or a TBPM group. The primary endpoint was the effect of TBPM on BP control after 3 months of monitoring.

The local ethical committee of lower Saxony approved the study and written informed consent was obtained from each patient. Major inclusion criteria were age: 16– (parental consent) 80 years, and ABPM mean value: $>130/80$ mm Hg ($>125/75$ mm Hg if diabetes mellitus and/or renal insufficiency), no treatment with an angiotensin receptor blocker. Major exclusion criteria were secondary hypertension, malignant hypertension, cerebrovascular incidents or hypertensive encephalopathy, stroke within the last 6 months, pheochromocytoma, acute or terminal renal failure, potassium <3.5 mmol l^{-1} or >5.5 mmol l^{-1}, untreated diabetes mellitus, untreated hyperthyroidism or hypothyroidism, pregnancy and contraindication against treatment with an AT1-receptor antagonist.

At month 0 the patient received 75 up to 300 mg irbesartan once or twice daily depending on the baseline ABPM BP value and circadian BP rhythm.[18–22] Both groups were instructed to measure their home BP once daily. The standard care group were advised to contact the treating physician by phone or visit the office in case of side effects or a not sufficient BP reduction. Patients in the TBPM group were equipped with the Stabil-O-Graph of the IEM Ltd Corporation (I.E.M. GmbH, Germany). The Stabil-O-Graph is a fully automatic, clinically validated (AAMI/BHS) BP meter with an upper arm cuff, bluetooth interface and bluetooth compatible mobile phone. As soon as a patient completed successfully a measurement with the Stabil-O-Graph, the patients' BP data were transmitted from the mobile phone via short message service remote operating system, which decoded the contents and transmitted them by TCP/IP via a secured channel to the central database server (Figure 1). Different alarm criteria were defined for patients with or without diabetes mellitus and/or renal insufficiency defined as estimated GFR <60 ml per min (MDRD formula) (Table 1). If alarm criteria were met an alarm report was generated automatically and sent via e-mail to the physician who contacted the patient by phone to discuss the future treatment strategy (Figure 1). The physician had full access to all BP data from the individual patients stored in the database server. Every month all patients in the TBPM group received a report with all BP values and alarms stored in the database.

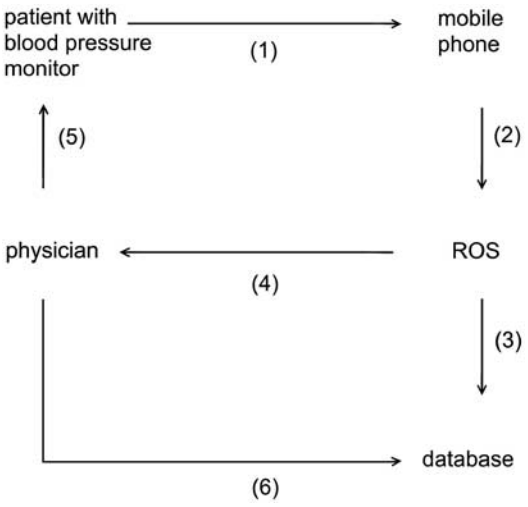

Figure 1 Scheme of data management. (1) The BP data from the patients was transmitted by the Stabil-O-graph via Bluetooth to a mobile phone, (2) the mobile phone sent the encrypted data via short message service to theremote operating system, the remote operating system decoded the data and transmitted it to a central data base, (4) if alarm criteria were met, an alarm report was sent via e-mail to the physician, (5) who contacted the patient by phone to resolve problems of compliance, and adapted medication if required, (6) the physician was able to access the data and to administer it.

After 3 months, the patients returned for a second scheduled 24-h ABPM. The primary endpoint was the effect of TBPM on the change in the mean 24-h ABPM. 24-h ABPM was collected at baseline and at 3 months using Mobil-O-Graph (I.E.M.). BP measurement was automatically performed every 15 min during daytime (0700 to 2200 hours) and every 30 min during nighttime (2200 to 0700 hours). BP telemonitoring was performed using Stabil-O-Graph and I.E.M. e-health service (I.E.M). The following BP parameters were collected: Systolic and diastolic mean BP, dipping (mean of the night/mean of the day *100–100)*−1), pulse pressure (systolic BP minus diastolic BP). Secondary endpoints were the

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effect of TBPM on BP dipping behavior and the rate of patients who reached the BP target.

After the second 24-h ABPM measurement both groups received standard care and the irbesartan dose was adjusted as required.

Additionally, the number of interventions (visits and telephone contacts), change and dosage of irbesartan, as well as the number of antihypertensives used were included in the analysis.

The following safety and efficiency parameters were measured

Creatinine (mg dl^{-1}), sodium (mg dl^{-1}), potassium (mg dl^{-1}), cholesterol (mg dl^{-1}), triglycerides (mg dl^{-1}), uric acid (md dl^{-1}) and hemoglobin (g dl^{-1}) were measured in serum at baseline and at 3 months. The urine was collected for 24 h at baseline and at the same time points and used to calculate the creatinine clearance (ml min^{-1} per 1.73 m^2), and also for 24 h proteinuria is measured. Additionally, eGFR was calculated using the abbreviated MDRD formula.

Table 1 Alarm criteria

	Without diabetes mellitus and/or renal insufficiency	*With diabetes mellitus and/or renal* insufficiency
Hypertension alarm		
Single BP	> 160/110 mm Hg	> 150/100 mm Hg
Mean BP during last 5 days	> 135/85 mm Hg	> 130/80 mm Hg
Hypotension alarm		
Single BP	< 90/50 mm Hg	
Mean BP during last 5 days	< 100/60 mm Hg	
No data transmission	>3 days	

Abbreviation: BP, blood pressure.
Renal insufficiency defined as eGFR <60 ml min^{-1} per 1.73 m^2 using MDRD formula.

Statistics

The analysis was carried out with Microsoft Excel 2002 and SSPS 16. For assessing significance, paired *t*-test with two-sided distribution were used to compare changes in one group and *t*-test for two samples with equal variance with two-sided distribution were conducted for comparison of the results of the two treatment arms. A *P*-value <0.05 was considered to be significant.

Results

Patients

Overall 60 persons, 30 patients in both study arms, with not sufficiently controlled hypertension were included using ABPM criteria according to ESH/ESC guidelines (Table 2). Three patients did not finish the 3-month study period and a second ABPM measurement was not obtained. One patient stopped the study because a close relative died, a second patient developed hypotension and further diagnostic criteria showed the presence of a significant renal artery stenosis, and a third patient developed myalgia during treatment with irbesartan and he was withdrawn from the study. As there were three dropouts, the intention-to-treat analysis included 60 patients, whereas per protocol analysis involved 57 patients.

Table 2 Baseline characteristics of patient population

Parameters	*TBPM group*	*Control group*
Group size (n)	30 (28)	30 (29)
Sex (m/f)	13/17 (12/16)	16/14 (15/14)
Mean age ± s.d., years.	54.7 ± 17.9 (55.9 ± 15.6)	56.2 ± 17.4 (56.2 ± 17.4)
BMI	27.1 ± 7.9 (27.2 ± 8.0)	27.3 ± 8.1(27.0 ± 7.8)
1st ABPM: mean BP ± s.d., mm Hg	142.8 ± 11.1/82.8 ± 10.4 (142.8 ± 11.1/82.8 ± 10.4)	141.4 ± 12.6/82.1 ± 6.5 (142.5 ± 13.5/82.6 ± 6.5)
Mean daytime BP ± s.d., mm Hg	145.2 ± 11.5/84.3 ± 11.0	144.6 ± 12.7/84.8 ± 7.5
Mean nighttime BP ± s.d., mm Hg	136.6 ± 15.2/77.5 ± 10.8	130.7 ± 17.3/73.1 ± 6.2
Antihypertensives, mean number ± s.d.	3.6 ± 1.7	3.2 ± 1.8
Patients with (in %/n)		
ACE inhibitors	60.7/17	55.2/16
Irbesartan	100/28	100/29
Beta Blocker	57.2/16	48.2/14
Calcium channel blocker	53.6/15	48.2/14
Diuretics	50/14	44.8/13
Others	35.7/10	27.6/8
Patients with diabetes and/or renal insufficiency	14	17

Abbreviations: ABPM, ambulant blood pressure monitoring; BP, blood pressure; F, female; M, male; TBPM, telemetric blood pressure monitoring.
Composition of the study patient population. Shown are group size, distribution between sexes, mean age, mean body height and weight, mean BP in the 1st ABPM and the mean number of used antihypertensives with s.d. and after dropout in brackets.

ABPM

In the control group mean 24-h ABPM systolic BP decreased from 141.4 ± 12.6 to 131.6 ± 11.8 ($P<0.001$) and diastolic BP from 82.1 ± 6.5 mm Hg to 75.1 ± 8.2 mm Hg ($P<0.001$) mm Hg. In the TBPM group systolic BP decreased from 142.8 ± 11.1 mm Hg to 126.3 ± 6.3 ($P<0.001$) and diastolic BP from 82.8 ± 10.4 mm Hg to 73.6 ± 7.3 ($P<0.001$). During the 3-month study period the BP was lowered by −16.5/−9.2 mm Hg in the TBPM group and −9.8/−7.0 mm Hg in the control group (systolic $P=0.032$; diastolic $P=0.356$) (Figure 2).

In the control group the systolic and diastolic nighttime dipping was not changed significantly (0.2 ± 9.0/−1.1 ± 8.9%), whereas in the TBPM group a more pronounced systolic and diastolic (3.7 ± 10.3/4.6 ± 11.6%) BP dipping was noted.

In the control group the pulse pressure decreased from 59.3 ± 12.5 mm Hg to 56.6 ± 10.2; ($P=0.054$) and in the TBPM group from 60.7 ± 9.8 to 52.7 ± 9.0; ($P<0.001$) mm Hg. Accordingly, a mean change of −2.8 ± 7.4 mm Hg in the control group and −8.1 ± 6.1 mm Hg in the TBPM group was found ($P=0.004$) (Figure 3).

The BP target values were achieved by 54% of the TBPM group and by 35% of the control group. In patients without diabetes mellitus or renal insufficiency with an ABPM target <130/80 mm Hg 54% in the control group and 57% in the TBPM group achieved the BP target values. In contrast in patients with either of this diseases, who had an ABPM target of <125/75 mm Hg, only 19% in the control group and 50% in the TBPM group were able to achieve target values.

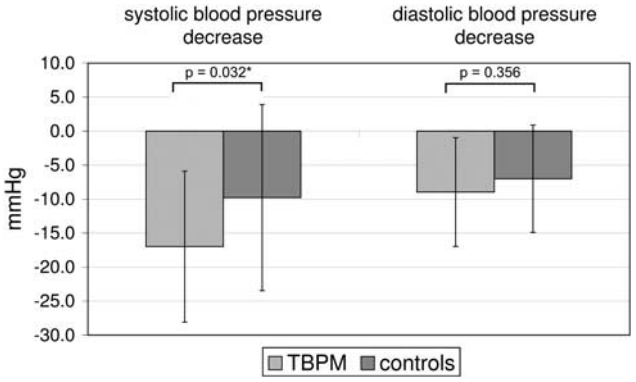

Figure 2 Effect of TBPM on 24-h ABPM. Differences between the control group and the TBPM group concerning the lowering of the mean systolic and diastolic BP during the study. Significant data is marked with *.

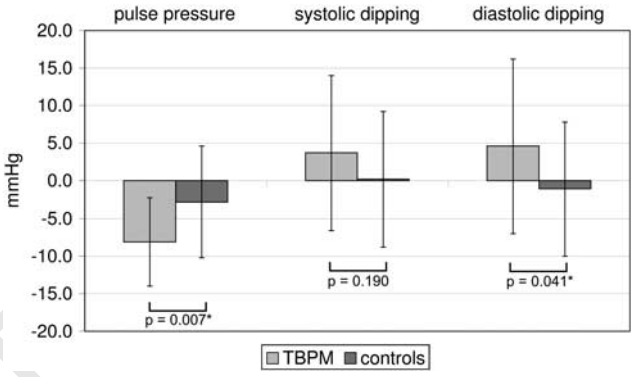

Figure 3 Effect of TBPM on BP parameters. Differences between the control group and the TBPM group concerning the lowering of the mean pulse pressure and dipping during the study. Significant data are marked with *.

Pharmaceuticals

After the baseline 24-h ABPM the patients were prescribed an average irbesartan dose of 233 ± 142 mg in the TBPM group and 220 ± 125 mg in the control group. During the following 3 months, the irbesartan dose was raised by 142 ± 159.9 to 375.0 ± 187.0 mg in the TBPM group ($P<0.001$) and by 2.6 ± 64.9 to 222 ± 147 mg ($P=0.832$) in the control group. The dose adjustment between the two groups was significantly different ($P<0.001$) (Figure 4). After the second 24-h ABPM at month 3, the irbesartan dosage was raised by an additional 64.7 ± 123.1 mg to 287.1 ± 184.8 mg in the control group ($P=0.008$). In the TBPM group no change of dosage was performed after the second ABPM. At the start of the study, the patients received 3.6 ± 1.7 different antihypertensives in the TBPM group and 3.2 ± 1.8 in the control group including treatment with irbesartan. No significant change was observed during the study period.

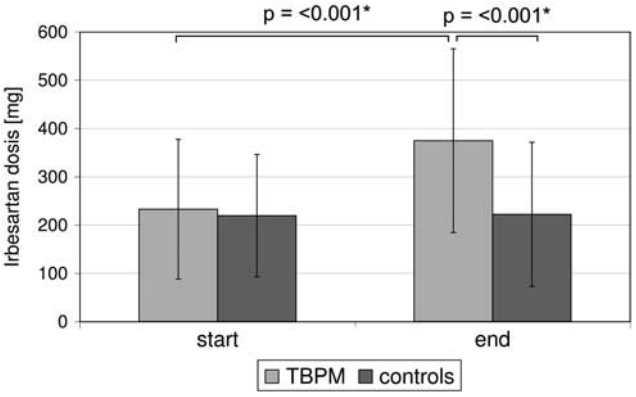

Figure 4 Irbesartan dosage. Differences between the control group and the TBPM group concerning the mean irbesartan dosage (mg) during the study. The dosages are shown from the beginning and the end of the study. Significant data are marked with *.

Telemetry and interventions

Analysis of the average BP in the TBPM group revealed, that the BP decreased every month. For systolic BP 1st month: 135.5 ± 10.5 mm Hg; 2nd month: 131.5 ± 9.6 mm Hg (−4.0 mm Hg; $P=0.016$); 3rd month: 130.4 ± 10.0 mm Hg (−1.1 mm Hg;

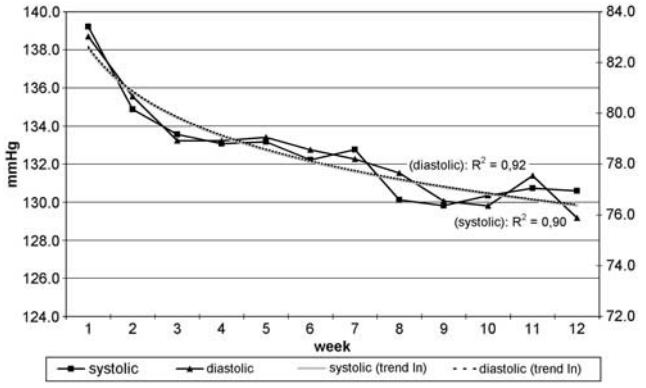

Figure 5 BP response in the TBPM group. Weekly average of the systolic and diastolic BP in the TBPM group during the 3-month survey. Logarithmic trendlines with associated coefficient of determination (R^2) is also shown.

$P = 0.387$) and for diastolic BP 1st month: 80.3 ± 7.2 mm Hg; 2nd month: 77.8 ± 6.6 mm Hg (-2.6 mm Hg; $P = 0.007$); 3rd month: 6.9 ± 6.5 (-1.5; $P = 0.042$) decrease was observed (Figure 5). Concerning therapy changes, the following number of changes in the irbesartan dose were made: in the 1st month $0.9 \pm 1.0/0.0 \pm 0.0$, in the 2nd month $0.5 \pm 0.7/0.0 \pm 0.2$ and in the 3rd month $0.3 \pm 0.7/0.0 \pm 0.2$ in the TBPM group and the control group, respectively.

In the TBPM group, the average number of interventions (telephone contacts) were 6.9 ± 5.5 in the 1st month, 5.7 ± 4.4 in the 2nd month and 6.0 ± 4.6 in the 3rd month. In contrast, in the control group 0.0 ± 0.0 interventions were performed in the 1st and 2nd month and 0.1 ± 0.3 in the 3rd month. The overall acceptance of the telemetric study design was high, 60 of 62 initially pre-screened patients agreed to participate in this study.

Laboratory results

Baseline and final laboratory results were available for 26 patients of the TBPM group and 28 patients of the control group. No significant difference was observed with one exception. The TBPM group showed a significant decrease of total cholesterol from 212.6 ± 41.5 mg dl^{-1} to 204.4 ± 48.2 mg dl^{-1}, $P = 0.036$).

Discussion

In this study, we demonstrate that the value of TBPM can be enhanced by using standardized alarm algorithms, which will inform the physician automatically about alterations in the BP control. By using this technique, we were able to demonstrate that a faster control of BP to target values is possible. In both groups the systolic and diastolic BP was lowered significantly during the 3-months treatment period by adding irbesartan to the pre-existing medication. Keeping in mind that patients in this study were pre-treated with averaged more than three antihypertensive drugs 60.7% in the TBPM group and 55.2% in the control group were already receiving ACE inhibitors when irbesartan was added on. Taking into account our study was performed and designed before the results of the ONTARGET study it has to be remarked that combination therapy with ACE inhibitors and ARBs is generally not recommended as standard therapy in essential hypertension. Nevertheless ONTARGET was not designed as a hypertension intervention study[23,24] and it has been shown, that a combination of ARB and ACE inhibitors leeds to an additional BP reduction compared with an ARB or ACE inhibitor application alone.[25,26]

However, the BP reduction was more pronounced in the TBPM group due to a faster up-titration of the irbesartan dosage. Furthermore, more patients in the TBPM group (54 vs 35%) achieved the desired 24-h ABPM BP target within 3 months. The advantage of the telemetric monitoring was even more apparent in the subgroup of patients with diabetes and/or renal insufficiency (50 vs 19%) who have a stricter BP target. Thus, alarm –criteria-based telemetric monitoring seems to be a method that facilitates the achievement of the desired BP values of the ESH/ESC guidelines.[6]

Evidence from several clinical trials suggests that a faster and better control of BP will translate into a reduction of cardiovascular and renal events. In the VALUE study a better BP control within the first 3 months was associated with a lower cardiovascular event rate and the ESH/ESC has adapted this recommendation in their guidelines.

The main reason for the better BP control in the TBPM group is surely the faster up-titration of the irbesartan dosage. This is also reflected in the number of therapy changes, which were necessary to enable a better adjustment of the TBPM group. Because of the fact, that the physician was alarmed, when the BP was out of bounds or the patient has not measured his/her BP within the last 3 days an individual and rapid intervention was possible with the chance to adapt the medication dose as required. Therefore, it is not surprising, that already in the first two treatment months the majority of the BP-lowering effect was achieved in the TBPM arm. Additionally, it can be assumed that the greater number of interventions led to a better patients' compliance in the TBPM group. Non-compliance could be identified directly, by counting the number of required BP measurements and indirectly, for example by recognizing sudden BP spikes in a well-treated stable patient. Those patients were reminded of the intake of their medication. A direct positive effect of TBPM on BP control has been previously reported,[27] probably due to an optimized compliance.[28,29]

The greater number of measurements during dosage titration gives the physician a higher certainty to act on. This was confirmed by the change of

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dosages after the 2nd ABPM. Though a raise of dosage was necessary in the control group because of a not sufficient BP control, it was not required to the same extent in the TBPM group. Thus TBPM seems to be superior concerning a quick and practical up-titration of antihypertensive drug dosage.

The split of the overall dosage of irbesartan into the morning and evening, for patients lacking dipping, seems to make sense. The higher titration and the associated evening intake of irbesartan yielded an explicitly better dipping in the TBPM group. It is important to recognize that the BP in the early morning is associated with vascular risk. Lowering of BP by an evening dose of medication contributes to the prevention of hypertensive incidents in the early morning.[30]

A significant improvement of renal function or proteinuria by irbesartan treatment as demonstrated in other studies[31] could not be shown. A reason for that could be the relatively short period of observation, the concomitant treatment with an ACE inhibitor by 50% of patients and the small number of patients. The administration of up to 600 mg irbesartan was safe, as it has been previously shown in other studies.[21]

This study's defined alarm criteria/algorithms proved to be practicable. A good correlation between morning TBPM readings and the mean 24-h BP at month 3 could be shown. This is clinical important, as the morning readings reflects the most critical period of BP characteristics within 24 h concerning the occurrence of cerebrovascular incidents.[8]

The use of TBPM seems to allow the physician to work safer and to enable an earlier identification of insufficiently treated patients providing the possibility to intervene and counteract promptly in the form of a change of therapy if necessary. Symptoms of hypertension or hypotension can be harmonized with the collected data with the aid of consultations by phone. In practice, TBPM can be seen as a reasonable addition to existing BP-measurement methods, especially ABPM, if alarm algorithms are followed by medical intervention. The diagnostic gap especially at the beginning or change of a patient's therapy can be bridged and the time between consultation can be extended, and a control ABPM measurement can be postponed.[32]

Concerning the collected data and required standards of the new ESH/ESC guidelines, the following procedure of hypertension management can be recommended: for discovering and evaluating the severity of the disease an ABPM should be carried out.[33] If the result of that ABPM is not optimal, a period of 8 weeks including 'interventional TBPM' for titration of dosage should be performed.

Patient acceptance concerning TBPM in this study was high, consistent with results from other studies.[17] TBPM was well accepted due to the fact that the technique is easy to use and reliable. Even elderly patients were confident in the usage of the TBPM device after an instruction period of 10 min. Physician's feedback by phone was also received extremely positive and it was not considered as annoying but rather helpful.

The question of whether TBPM has also economic advantages, with respect to the demographical development, can only be answered with the help of more comprehensive health economics studies. In the end, possibly long-term effects of TBPM must be examined in other studies. This study could help to work out a consistent strategy for handling TBPM BP data in line with the most recent publications of ABPM.[8,9]

In summary, TBPM is qualified for an optimized, individualized and precise BP adjustment. By means of technical reliability and user friendliness of the software and the set-up of devices in this study a high patient acceptance was made possible. TBPM enables a better BP monitoring than AMBP in standard outpatient care.

What is known about this topic

- Far less than half of the diagnosed hypertensive patients are treated adequately and reach target BP values.[4]
- Especially in high-risk patients intensive monitoring including frequently office visits or new techniques to monitor home BP is required.[6]

What this study adds

- TBPM enables a better BP monitoring than office BP in standard outpatient care in an ABPM controlled study design.
- This study's defined alarm criteria/algorithms proved to be practicable.

Conflict of interest

H Haller has received honoraria from Daiichi-Sankyo, Sanofi-Aventis, Amgen, Roche, Recordati, Takeda, Astra-Zeneca, Berlin-Chemie and Novartis. J Menne has received honoraria from Daiichi-Sankyo, Novartis and Berlin Chemie. The other authors declare that they have no conflict of interest with this paper.

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