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**CLINICAL RESEARCH**

# Interventions aimed to increase average 24-h systolic blood pressure reduce blood pressure drops in patients with reflex syncope and orthostatic intolerance

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**Aims** Systolic blood pressure (SBP) drops recorded by 24-h ambulatory blood pressure (BP) monitoring (ABPM) identify patients with susceptibility to reflex syncope and orthostatic intolerance. We tested the hypothesis that treatments aimed to increase BP (reassurance, education, and lifestyle measures plus pharmacological strategies) can reduce SBP drops.

**Methods and results** This was a multicentre, observational proof-of-concept study performed in patients with reflex syncope and/or orthostatic intolerance and with SBP drops on a screening ABPM. Among 144 eligible patients, 111 underwent a second ABPM on average 2.5 months after start of treatment. Overall, mean 24-h SBP increased from 114.1 ± 12.1 to 121.4 ± 14.5 mmHg ($P < 0.0001$). The number of SBP drops <90 and <100 mmHg decreased by 61%, 46% during daytime, and by 48% and 37% during 24-h period, respectively ($P < 0.0001$ for all). The dose–response relationship between difference in 24-h average SBP increase and reduction in number of SBP drops reached a plateau around ∼15 mmHg increase of 24-h SBP. The reduction in SBP drop rate was consistent and significant in patients who underwent deprescription of hypotensive medications ($n = 44$) and in patients who received BP-rising drugs ($n = 67$).

**Conclusion** In patients with reflex syncope and/or orthostatic intolerance, an increase in average 24-h SBP, regardless of the implemented strategy, significantly reduced the number of SBP drops and symptom burden. A 13 mmHg increase in 24-h SBP appears to represent the optimal goal for aborting the maximal number of SBP drops, representing a possible target for future interventions.

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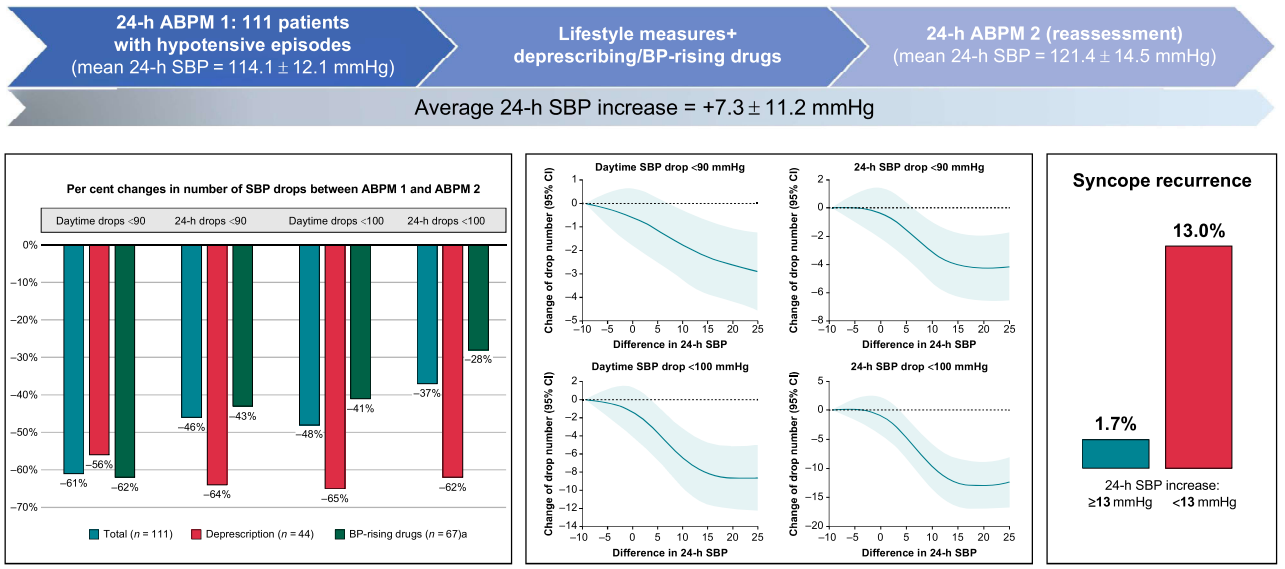
## Graphical Abstract




Interventions aimed to increase average 24-h systolic blood pressure reduce blood pressure drops in patients with reflex syncope and orthostatic intolerance

**Keywords** Hypotensive reflex syncope • Orthostatic intolerance • 24-h ambulatory blood pressure monitoring • Blood pressure variability

## What's new?

- Systolic blood pressure (SBP) drops recorded by 24-h ambulatory blood pressure monitoring (ABPM) identify patients with susceptibility to reflex syncope and/or orthostatic intolerance and may predict a hypotensive mechanism of syncope.
- We tested the hypothesis that treatments aimed to increase blood pressure can reduce SBP drops and hopefully prevent syncopal recurrences.
- Mean 24-h SBP increased from 114.1 ± 12.1 mmHg before to 121.4 ± 14.5 mmHg during treatment, regardless of the implemented therapeutic strategy.
- The number of SBP drops <90 and <100 mmHg decreased by 61%, 46% during daytime, and by 48% and 37% during 24-h period.
- The dose–response relationship between difference in 24-h average SBP increase and reduction in number of SBP drops reached a plateau around ∼15 mmHg increase of 24-h SBP.
- A 13 mmHg increase in 24-h SBP appears to represent the optimal goal for aborting the maximal number of SBP drops, representing a possible target for future interventions

# Introduction

In patients with reflex syncope and orthostatic intolerance, identification of the haemodynamic mechanism underlying loss of consciousness represents the first step towards understanding and prevention of syncope recurrence.[1] Detection of hypotension as a potent trigger mechanism of syncope may prompt deprescription of hypotensive medications or prescription of blood pressure (BP) rising therapy to counteract the risk of excessive BP falls. Yet, diagnosing a hypotensive mechanism may be challenging, due to the extreme difficulty in obtaining BP measurements during spontaneous syncopal episodes. A recent study from our group investigated the use of 24-h ambulatory BP monitoring (ABPM) and demonstrated that reflex syncope patients more frequently show daytime and 24-h systolic (S) BP drops on ABPM compared with non-syncopal individuals.[2] Daytime episodes of systolic blood pressure (SBP) <90 and <100 mmHg were observed in 40% of the study cohort. These BP values were identified as the susceptibility markers which best discriminated patients with reflex syncope from controls. These drops can occur independently of the presence of symptoms. Systolic blood pressure drops on ABPM could represent manifestations of hypotensive susceptibility, i.e. a predisposition to hypotensive episodes potentially leading to reflex syncope, and may contribute to identify patients with the so-called hypotensive phenotype of reflex syncope. In patients with hypotensive susceptibility, compensatory mechanisms are usually activated to prevent excessive SBP drops[3] and to preserve organ perfusion. Systolic blood pressure drops probably manifest when compensatory mechanisms temporarily fail and may potentially evoke reflex syncope or symptoms of orthostatic intolerance in the presence of typical triggers and circumstances. We thus inferred that, in patients affected by reflex syncope, daytime SBP drops detected by ABPM may predict a hypotensive mechanism of syncope.[2] The hypothesis of the current proof-of-concept study was that interventions aimed to increase arterial BP could reduce SBP drop rate on ABPM. If this hypothesis is true, then a therapeutic strategy aimed to eliminate SBP drops by adequately increasing arterial BP should allow to prevent syncopal recurrences.

# Methods

SynABPM 2 is a multicentre, prospective, observational proof-of-concept study performed in patients with reflex syncope and/or orthostatic intolerance and significant SBP drops on ABPM (ABPM 1), who received treatments aimed to increase average BP and abort or reduce hypotensive events. Eligible patients underwent a second ABPM (ABPM 2) within 6 months of the first examination, and the results of the two ABPMs were

compared to assess the effects of therapeutic interventions. The study was approved by the Ethics Committees of the participating centres.

## Inclusion criteria

Patients who met the following criteria were deemed eligible for the study:

(1) Established diagnosis of reflex syncope and/or orthostatic intolerance, i.e. hypotensive symptoms while standing, not associated with loss of consciousness
(2) Greater than or equal to 1 daytime SBP drop < 90 mmHg or ≥2 daytime SBP drops < 100 mmHg recorded by an ABPM performed during the routine work-up of syncope in the hospital participating in the study[2]
(3) Having received one or more of the following interventions aimed to increase arterial BP: (i) education and lifestyle measures, i.e. counselling on avoidance of triggers and predisposing situations for hypotension and syncope, early recognition of prodromal symptoms, and strategies for syncope prevention, i.e. lying down, prompt activation of counter-pressure manoeuvres, and increase in water and salt intake; (ii) drug deprescribing, i.e. reduction or withdrawal of hypotensive medications including antihypertensive drugs and psychoactive drugs with known hypotensive effects[4]; and (iii) prescription of BP-rising (vasoconstricting/volume expanding) drugs, mainly consisting of fludrocortisone and midodrine, in patients with constitutional or acquired hypotension who were not receiving any antihypertensive medication

In complying with the European Society of Cardiology (ESC) syncope guidelines,[5] reflex syncope was diagnosed when the clinical features were consistent with a reflex mechanism and competing diagnoses had been excluded. Tilt testing was performed to confirm the diagnosis when reflex syncope was suspected but not established after the initial assessment. Patients with constitutional hypotension, defined in accordance with the literature as 24-h SBP below the lowest 5% confidence interval (CI) of a general population,[6,7] i.e. SBP ≤105 mmHg for males and ≤98 mmHg for females, were also eligible and were included in the study. Carotid sinus massage and tilt testing were not mandatory for enrolment.

## Exclusion criteria

(1) Age < 18 years
(2) Symptomatic orthostatic hypotension, defined as a symptomatic fall in SBP ≥ 20 mmHg or a SBP decrease to <90 mmHg, as per the ESC guidelines[3]
(3) Competing causes of syncope (i.e. syncope due to arrhythmias and cardiac structural diseases and non-syncopal causes of transient loss of consciousness as defined by the ESC guidelines on syncope)[4]
(4) Severe cardiac disease, previous stroke, or transient ischaemic attack

## Study objectives (endpoints)

The study addressed three main objectives:

(1) To investigate whether interventions aimed to increase average 24-h SBP can reduce SBP drops on ABPM
(2) To assess whether the reduction of SBP drops is directly correlated with the increase in average 24-h SBP
(3) To identify the magnitude of 24-h SBP increase allowing to achieve an optimal reduction in SBP drops

As a secondary objective, we investigated the short-term changes in hypotensive symptoms.

## Study outcome measures

The following data were collected and compared between ABPM 1 and ABPM 2:

- Average 24-h SBP, diastolic BP, and heart rate
- Average daytime and nighttime SBP
- Number of daytime SBP drops < 90 mmHg
- Number of 24-h SBP drops < 90 mmHg
- Number of daytime SBP drops < 100 mmHg
- Number of 24-h SBP drops < 100 mmHg
- Effect of interventions on hypotensive symptoms reported in the period between ABPM 1 and ABPM 2 (vs. symptoms during the period preceding ABPM 1), assessed according to a four-grade semiquantitative subjective assessment

Systolic blood pressure drops consisted of single SBP measures <100 or <90 mmHg.[2] Taking into considerations possible differences in actual sleep time, daytime was defined as the period between 07:00 a.m. and 11:00 p.m..

## Statistical analysis

Continuous variables are reported as mean and standard deviation (SD) or median and interquartile range (IQR) in case of not normally distributed data. Categorical variables are shown as absolute and relative frequencies. Pre–post comparisons of continuous variables are performed by means of the *t*-test paired or Wilcoxon ranked-signed test, as appropriate. Moreover, the dose–response relationship between change in 24-h SBP and change in the number of SBP drops was investigated by means of restricted cubic splines. In brief, a cubic spline is essentially a piecewise cubic polynomial, where the number of 'pieces' is dictated by the number of windows used, identified by specific points (knots) on the range of change of 24-h SBP. In each window, a cubic polynomial was fitted in observed points.[8] We chose five windows considering as knots 5th, 35th, 65$^{th}$, and 95th percentile of change SBP 24 h. Syncope recurrence was analysed by mean of the Kaplan–Meir survival curves, which were compared using the log-rank test. All tests were two-sided and *P*-values < 0.05 were considered statistically significant. All analysis was conducted using SAS 9.4 (SAS Institute, Cary NC, USA) and R (version 4.2.3, Vienna, Austria).

In the absence of previous data, a sample size of 104 patients would allow to correlate the difference of 24-h SBP between ABPM 1 and ABPM 2 with the difference in the number of SBP drops, with a two-sided 95% CI with a width equal to 0.25 when the estimate of Pearson's product–moment correlation is 0.6.

# Results

## Characteristics of the study sample

Among 144 eligible patients who had undergone ABPM 1 in the period January 2022 to April 2023, 111 underwent ABPM 2 and were included in the analysis. The median time interval between ABPM 1 and ABPM 2 was 2.5 months (interquartile range 1.3; 4.3). Patients' clinical characteristics are shown in *Table 1*. All patients received instructions on education and lifestyle measures. Deprescription of hypotensive drugs was recommended in 44 hypertensive patients, and BP-rising (vasoconstricting/volume expanding) therapy was prescribed in 67 patients with constitutional or acquired hypotension (see Supplementary material online, *Tables S1* and *S2*). Four participants from the deprescription group and 13 from the BP-rising drugs group did not modify medical therapy between ABPM 1 and ABPM 2. These patients were nevertheless included in the analysis. During the study period, treatments were well tolerated without side effects. At the time of ABPM 2, the patients were asked to rank their quality of life and to compare with that at the time of ABPM 1. Overall, 62% of patients declared a moderate or substantial symptom improvement between ABPM 1 and ABPM 2 in both study groups (see Supplementary material online, *Figure S1*).

## Comparison between ABPM 1 and ABPM 2

In the overall sample, ABPM 2 showed a 7.3 ± 11.2 mmHg increase of 24-h SBP (from 114.1 ± 12.1 to 121.4 ± 14.5 mmHg), while the number of daytime and 24-h SBP drops <90 and <100 mmHg decreased by 61% and 46% and by 48% and 37%, respectively (*Table 2* and *Figure 1*). Consistent and significant changes were reported in both the deprescription and BP-rising group (*Figure 1* and Supplementary material online, *Tables S3* and *S4*) and in younger and older patients

**Table 1** Characteristics of the study sample

| | Overall sample $n = 111$ | Deprescription $n = 44$ | BP-rising drugs $n = 67$ |
|---|---|---|---|
| Mean age, *years* | 55.3 ± 21.8 | 73.6 ± 9.6 | 43.2 ± 18.9 |
| Females, *n (%)* | 77 (69%) | 30 (68%) | 48 (72%) |
| History of syncope, *n (%)* | 92 (83%) | 44 (100%) | 51 (76%) |
| Syncope episodes in the lifetime, *median (IQR)* | 7 (2;10) | 3 (2;8) | 10 (5;10) |
| Syncope episodes/last year, *median (IQR)* | 3 (1;5) | 2 (1;3) | 3 (2;5) |
| Presyncopes and orthostatic intolerance, *n (%)* | 60 (54%) | 8 (18%) | 52 (78%) |
| Triggers, *n (%) (may be multiple)* | | | |
| Orthostatic | 91 (82%) | 36 (82%) | 55 (82%) |
| Emotional | 11 (10%) | 2 (5%) | 9 (13%) |
| Situational | 20 (18%) | 13 (30%) | 7 (10%) |
| Undetermined | 11 (10% | 3 (7%) | 8 (12%) |
| ECG abnormalities, *n (%)* | 22 (20%) | 10 (23%) | 12 (18%) |
| Structural heart disease | 16 (14%) | 12 (27%) | 4 (6%) |
| Office SBP, mean ± SD (mmHg) | 125.6 ± 20.0 | 135.6 ± 20.3 | 118.7 ± 16.7 |
| Tilt testing, *n (%)* | 59 | 22 | 37 |
| Positive, mixed form | 32 (54%) | 15 (35%) | 17 (46%) |
| Positive, cardioinhibitory form | 4 (7%) | 0 (0%) | 4 (11%) |

BP, blood pressure; ECG, electrocardiogram; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation.

**Table 2** ABPM 1 and ABPM 2 results in the overall sample ($n = 111$ patients)

| | ABPM 1 | ABPM 2 | Difference | *P* value |
|---|---|---|---|---|
| 24-h SBP, mmHg *mean ± SD* | 114.1 ± 12.1 | 121.4 ± 14.5 | +7.3 ± 11.2 | <0.0001 |
| Daytime SBP, mmHg *mean ± SD* | 115.9 ± 11.6 | 124.0 ± 14.0 | +8.1 ± 11.7 | <0.0001 |
| Nighttime SBP, mmHg *median (IQR)* | 107 (98–116) | 113 (103–124) | +5 (−3 to 13)[a] | <0.0001 |
| 24-h DBP, mmHg *median (IQR)* | 68 (64–73) | 71 (66–77) | 3 (0–7) | <0.0001 |
| 24-h heart rate, b.p.m. *median (IQR)* | 72 (63–80) | 70 (64–78) | −2 (−5 to −3)[b] | 0.041 |
| Daytime SBP drop <90 mmHg | | | | |
| Total number | 294 | 116 | −61% | |
| Median number (IQR) | 1 (0–4) | 0 (0–1) | −1 (−2 to 0) | <0.0001 |
| 24-h SBP drops <90 mmHg | | | | |
| Total number | 541 | 294 | −46% | |
| Median number (IQR) | 3 (1–7) | 1 (0–4) | −1 (−4 to 0) | <0.0001 |
| Daytime SBP drop <100 mmHg: | | | | |
| Total number | 870 | 454 | −48% | |
| Median number (IQR) | 6 (2–11) | 2 (0–7) | −3 (−7 to −1) | <0.0001 |
| 24-h SBP drops <100 mmHg | | | | |
| Total number | 1447 | 913 | −37% | |
| Median number (IQR) | 11 (5–18) | 4 (1–12) | −4 (−9 to 0) | <0.0001 |

b.p.m., beats per minute; DBP, diastolic blood pressure; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation.
[a]Two patients missing.
[b]Three patients missing.

(above or below the median age of 58 years) (see Supplementary material online, *Table S5*).

To investigate the magnitude of 24-h SBP increase corresponding to the optimal reduction in SBP drop rate, we analysed the dose–response relationship between changes in 24-h SBP and changes in the number of SBP drops (*Figure 2*). While the reduction of daytime SBP drops < 90 mmHg was almost linearly correlated with the increase in 24-h SBP, the slope of the three other curves tended to flatten around

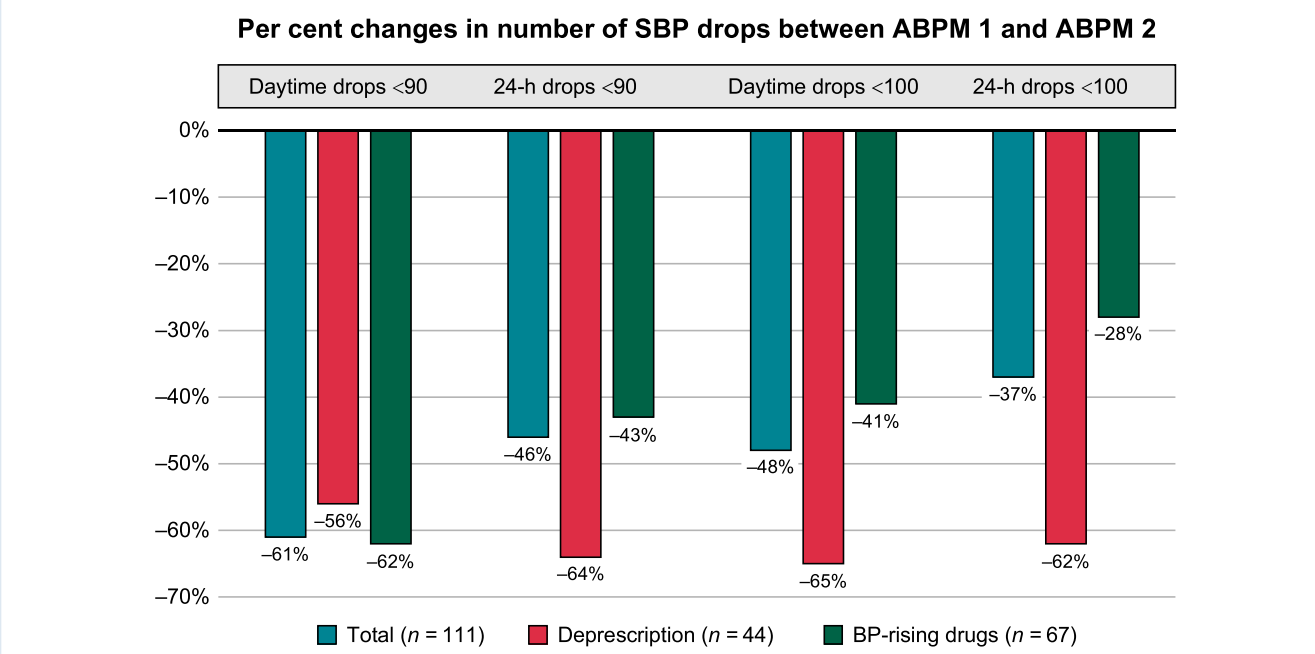



**Figure 1** Per cent changes in number of SBP drops recorded during ABPM 1 and ABPM 2. Intention-to-treat analysis.

~15 mmHg increase of 24-h SBP, suggesting that this value may correspond to the target 24-h cut-off SBP value achieving the optimal reduction in SBP drops. This finding was confirmed by the results shown in *Figure 3* and in Supplementary material online, *Table S6*. The study cohort was divided in two subgroups according to the median of the differences of 24-h SBP between ABPM 1 and ABPM 2. The two subgroups had similar baseline values of 24-h SBP on ABPM 1. On ABPM 2, the 24-h SBP increased by 13 mmHg (IQR 10 to 20) in the upper median subgroup and the number of all types of SBP drops decreased significantly. Conversely, in the lower median subgroup, 24-h SBP increased by 1 mmHg (IQR −4 to +3) and the reduction in the number of SBP drops was substantially less. The difference in the number of SBP drops between subgroups was significant for all four parameters (see Supplementary material online, *Table S6*). During the follow-up period, eight patients reported recurrence of syncope. Of these, 1 occurred among the 57 patients (1.7%) who had an increase of 24-h SBP ≥ 13 mmHg (from 112.8 ± 10.0 to 128.4 ± 13.1 mmHg) and 7 occurred among the 54 patients (13.0%) who did not (from 115.6 ± 13.9 to 114.1 ± 12.2 mmHg), log-rank $P = 0.06$ [hazard ratio: 0.17 (95% CI: 0.17–0.70)] (*Figure 4*).

## Discussion

The SynABPM 2 proof-of-concept study demonstrates that an increase in average 24-h SBP, regardless of applied interventional strategy, is associated with a significant reduction in the number of SBP drops on 24-h ABPM. An increase in 24-h SBP of ~13 mmHg seems to represent the most effective target for therapeutic interventions, allowing to achieve the optimal reduction of SBP drops. A trend towards syncope reduction was observed in the subgroup of patients who had an increase in 24-h SBP ≥ 13 mmHg compared with those who did not.

Recent research demonstrated that reflex syncope patients may have a labile haemodynamic homeostasis, which leads to chronic activation of compensatory mechanisms, i.e. increased vascular resistance and heart rate, aiming to counteract a predisposition to hypotensive episodes.[9,10] SynABPM 1 study[2] showed that up to 40% of patients with reflex syncope have SBP drops that have been identified as a marker of hypotensive susceptibility and a possible trigger of syncope with hypotensive mechanism.[2] In the present study that included only patients with SBP drops, the values of office BP were within the normal range in most cases (*Table 1*) and would not have allowed a diagnosis of hypotensive susceptibility. The present study shows that SBP drops are less likely to occur if 24-h SBP is maintained at higher levels, although still within the range of normotension. Higher BP levels can be achieved through lifestyle measures and deprescribing of hypotensive medications or prescription of vasoconstrictive and/or volume expanding drugs.

A large body of evidence speaks in favour of cardiovascular benefits associated with antihypertensive therapy, and, in recent years, additional data have been provided supporting even more aggressive BP lowering in hypertensive patients.[11,12] However, a meta-analysis clearly showed that the lower is the BP achieved by antihypertensive treatment, the higher is the number of patients discontinuing treatment because of side effects (including hypotension) and thus remaining without cardiovascular protection.[13] Despite the evidence that intensive treatment is associated with an increased risk of hypotension and syncope,[14] few clinical trials have investigated when and how medications should be discontinued or at least downtitrated in patients with hypotensive adverse events.[15] Most of existing studies focus on antihypertensive deprescribing in frailer, older adults,[16–18] while a paucity of data in this regard is available in patients with a history of syncope and hypotensive episodes.

In the STOP-VD trial,[19] older adults with hypotensive mechanism of reflex syncope were randomized to continue antihypertensive therapy or to receive deprescribing (i.e. withdrawal/reduction of antihypertensive medications) with a SBP target < 150 mmHg. The study results showed a reduced recurrence of syncope and presyncope in patients receiving deprescribing, with no increase in the risk of cardiovascular and neurological events. Consistently, the reduction or withdrawal of antihypertensive medications was found to increase the probability of recovery from orthostatic hypotension[20] and vasodepressive carotid sinus syndrome.[21] These findings suggest that hypotensive susceptibility modifies the risk/benefit ratio of antihypertensive therapy due to

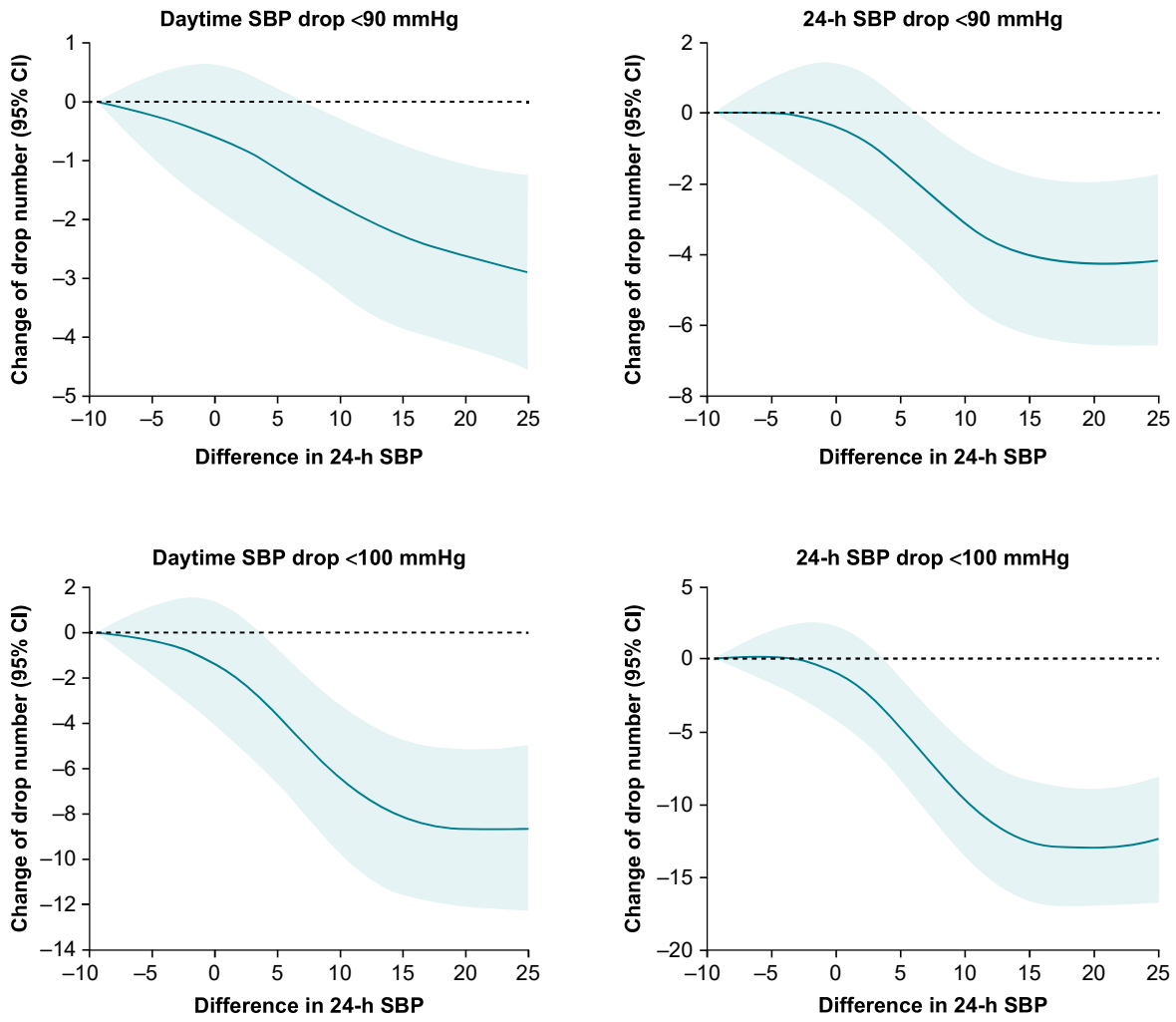



**Figure 2** The dose–response relationship between changes in 24-h SBP and changes in the number of SBP drops with relative 95% CIs.

increased predisposition to hypotension and syncope as important adverse events.[22] Therefore, patients with hypotensive susceptibility are likely to benefit from a more prudent treatment approach, avoiding intensive BP lowering. Consistently, in patients with hypotensive syncope, the ESC guidelines on syncope recommend reduction of hypotensive medications as a first-line treatment strategy together with patients' education and application of lifestyle measures in patients with hypotensive syncope mechanism.[5] However, evidence is lacking to guide revision of medical therapy in this clinical context. Moreover, although ABPM has been recommended as a diagnostic tool to investigate hypotension,[11] ABPM parameters that should guide treatment optimization remain currently unclear.

Systolic blood pressure drops on ABPM represent a marker of hypotensive susceptibility and might be useful to identify patients who likely benefit from a less intensive treatment strategy. The current SynABPM 2 study provides support for this hypothesis, showing a reduction in SBP drops and improvement of hypotensive symptoms when less intensive BP control was adopted. Moreover, the study provides useful indications to guide reduction of antihypertensive medications, suggesting a 13–15 mmHg increase in 24-h SBP as the most effective target, if acceptable from the cardiovascular risk perspective. The suggestion to reduce number and/or dose of antihypertensive drugs puts clinicians in front of a by no means banal dilemma.

Clinicians might be worried that reduction of antihypertensive therapy to prevent syncope could increase the risk of cardiovascular events. However, existing data indicate that antihypertensive deprescribing can be safely performed with hypertension remaining well controlled in a significant proportion of patients, particularly in the case of lower on-treatment BP values.[15,18,23–26] Moreover, it should be considered that a J-shaped relationship exists between BP and cardiovascular risk, with risk increasing at very low BP values, i.e. with SBP < 120 mmHg in some patients.[22] Although cardiovascular risk was not investigated in our study, patients assigned to deprescription showed appropriate BP control on ABPM 2, with 24-h SBP values remaining below the threshold associated with increased risk of mortality and CV events.[27]

Similarly, 24-h SBP increased from 110.1 to 116.4 mmHg in patients assigned to BP-rising interventions, thus remaining far below the cut-off corresponding to hypertension diagnosis and increased cardiovascular risk. Previous randomized studies in patients with severe and recurrent reflex syncope demonstrated positive effects of treatment with fludrocortisone and midodrine.[28,29] These drugs were often applied in our study as a pharmacological approach to increase BP, and our results are consistent with their efficacy in prevention of syncopal recurrences.[28–30] Similar results were also reported in individuals with constitutional hypotension receiving midodrine.[31]

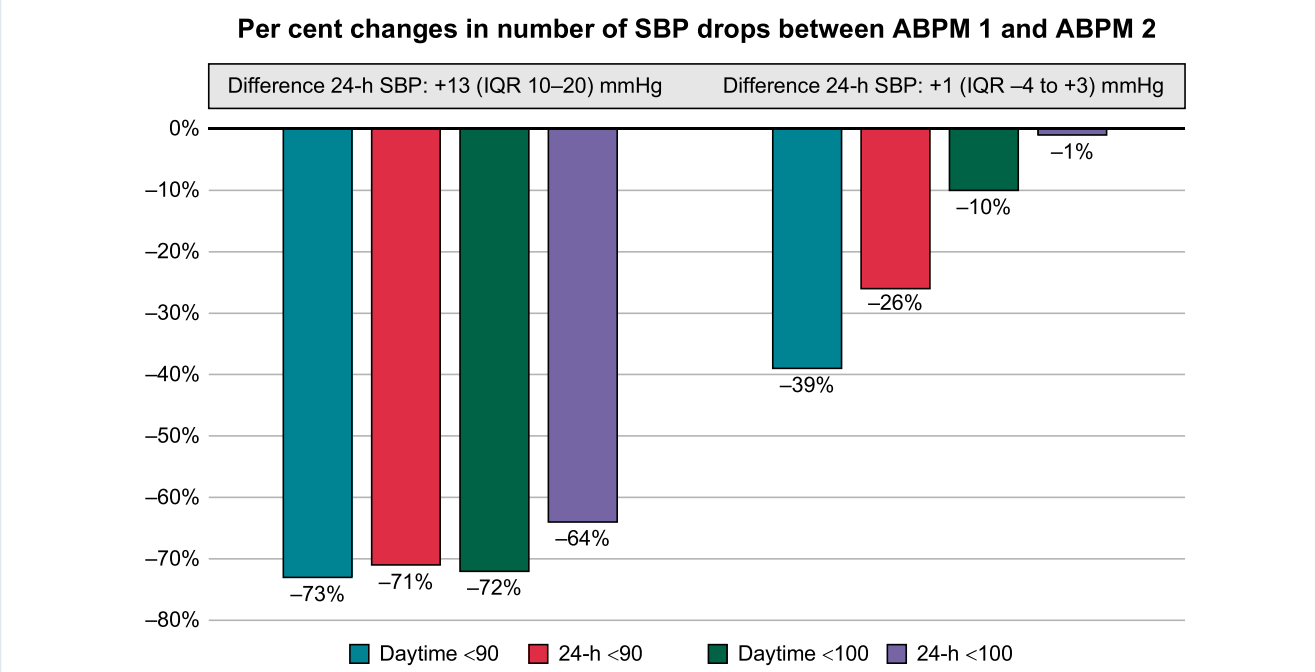



**Figure 3** Per cent changes in the number of SBP drops in two subgroups based on the median of the differences of 24-h SBP between ABPM 1 and ABPM 2. The difference in the number of SBP drops between subgroups was significant for all four parameters (see Supplementary material online, *Table S6*).

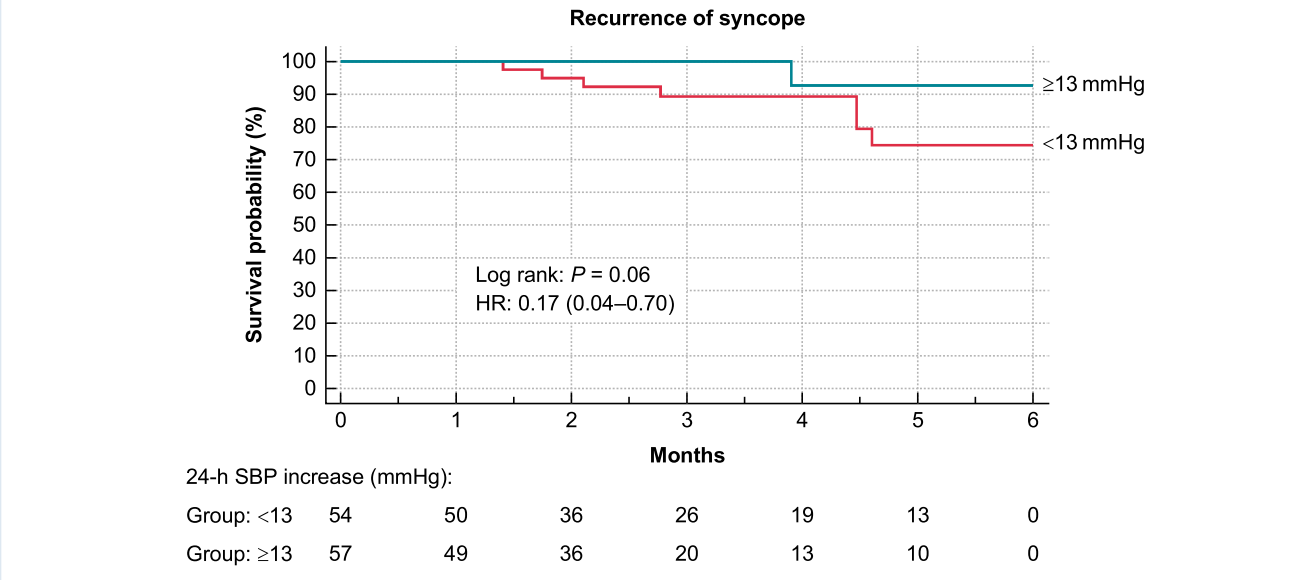



**Figure 4** Freedom from syncope recurrence in the period between ABPM 1 and ABPM 2 in the two subgroups of patients who had an increase of 24-h SBP ≥ 13 mmHg or <13 mmHg.

The present study confirms that ABPM plays a relevant role in the diagnostic work-up of syncope, particularly if reflex syncope with hypotensive mechanism is suspected after the initial assessment.[1] Yet, ABPM does not allow to investigate the presence of a cardioinhibitory component of reflex syncope that may coexist with hypotensive susceptibility and contribute to symptom recurrences. Therefore, it is advisable that ABPM is performed in the context of a more comprehensive cardiovascular autonomic function testing including also tilt testing and carotid sinus massage, if indicated.[32,33] Such approach would allow for a more precise assessment of haemodynamic phenomena underlying

loss of consciousness and for the development of effective treatment strategies to prevent syncope recurrences.[34,35,36]

## Clinical impact and perspectives

In the previous SynABPM 1 study,[2] we inferred that, in patients affected by reflex syncope, daytime SBP drops on ABPM predict a hypotensive mechanism of syncope. If this hypothesis is true, then a therapeutic strategy aimed to avoid SBP drops should be effective in preventing syncope recurrences. The SynABPM 2 study demonstrates that an increase of 24-h SBP, in whatever way it has been obtained, can reduce SBP drops and improve hypotensive symptoms. Even if the study was not designed to assess the efficacy of treatment, we observed a trend towards a great reduction of syncope recurrences in the patients who, at the time of ABPM 2, had an increase of 24-h SBP $\geq$ 13 mmHg compared with ABPM 1. Therefore, the results of the present study provide the background for a future prospective randomized controlled trial aimed at further supporting our proposal to avoid SBP drops at 24-h ABPM aimed at preventing reflex syncope and orthostatic intolerance.

## Limitations

Some limitations in this study must be acknowledged. We did not investigate possible changes in cardiovascular risk associated with 24-h SBP increase, and thus, we are unable to draw any conclusion on safety issues. Yet, the increase of 24-h SBP observed in our study was consistent with SBP changes reported in previous research on antihypertensive drug deprescribing,[20,25] where no significant risk of adverse events was described. Reproducibility of ABPM responses was not tested. While reproducibility of ABPM has been assessed in the literature,[37] there are no data regarding reproducibility of SBP drops. Treatment approaches were not standardized but rather based on clinical judgement and on routine practice of individual investigators.

# Conclusions

In patients with reflex syncope and/or orthostatic intolerance, treatment strategies increasing average 24-h SBP allowed to significantly reduce the number of SBP drops on ABPM as well as hypotension-related symptoms. A 13–15 mmHg increase of 24-h SBP seems to represent the most effective treatment goal to minimize SBP drops and, possibly, to prevent syncope recurrence and improve symptoms. This data pave the way to future randomized intervention trials that might test the actual ability to prevent syncope recurrence through removal of SBP drops over 24 h in a larger sample of patients with reflex syncope and/or orthostatic intolerance.

# Supplementary material

Supplementary material is available at *Europace* online.

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**Conflict of interest:** none declared.

## Data availability

The data sets generated during and/or analysed during the current study are available upon reasonable request (https://zenodo.org/badge/DOI10.5281zenodo.10439449/).

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# Supplementary data

**Supplementary Table S1.** Hypotensive medications during ABPM 1 and ABPM 2 in 44 patients assigned to deprescription group.

| | ABPM 1 | ABPM 2 | | |
|---|---|---|---|---|
| | | Withdrawal | Dose reduction | Unchanged |
| Total number of hypotensive drugs | 104 | 46 (44%) | 18 (17%) | 40 (38%) |
| Median number per patient (IQR) | 2 (1 to 3) | | | |
| -ACE-inhibitors | 17 | 8 | 3 | 6 |
| -ARBs-inhibitors | 19 | 5 | 5 | 9 |
| -Beta-blockers | 17 | 7 | 2 | 8 |
| -Ca-antagonists | 10 | 6 | 2 | 2 |
| -Alpha-blockers | 8 | 4 | 1 | 3 |
| -Diuretics | 18 | 12 | 3 | 3 |
| -Benzodiazepines | 5 | 2 | 1 | 2 |
| -Antidepressants | 4 | 1 | 0 | 3 |
| -SSRI/SNRI | 3 | 0 | 1 | 2 |
| -Opioids | 1 | 0 | 0 | 1 |
| -Trazodone | 1 | 1 | 0 | 0 |
| -Levo-Dopa | 1 | 0 | 0 | 1 |

ACE stands for Angiotensin-converting enzyme (ACE) inhibitors; ARB stands for angiotensin receptor blockers; SSRI stands for selective serotonin reuptake inhibitors; SNRI stands for serotonin and norepinephrine reuptake inhibitor.

**Supplementary Table S2.** Medications during ABPM 2 in 67 patients assigned to BP rising drugs.

| Drug | Patient number | Daily dose |
|---|---|---|
| Fludrocortisone, total | 39 | 0.5 mg (#3); 0.1 mg (#15); 0.2 mg (#21) |
| -Fludrocortisone alone | 32 | |
| Midodrine, total | 21 | 5 mg (#4); 7.5 mg (#12); 10 mg (#3); 20 mg(#2) |
| - Midodrine alone | 14 | |
| Fludrocortisone + Midodrine | 7 | |
| Pyridostigmine | 1 | 20 mg |
| No BP rising drugs* | 13 | |

*Nine of these patients received ivabradine to counteract tachycardia in POTS patients

**Supplementary Table S3.** ABPM results in 44 patients assigned to deprescription according to the Intention-to-treat principle.

| | ABPM 1 | ABPM 2 | Difference | P value |
|---|---|---|---|---|
| Mean 24-hour SBP, mmHg | 120.2±10.8 | 129.0±14.0 | +8.8±14.1 | 0.0001 |
| Daytime SBP, mmHg | 121.7±11.3 | 131.9±13.9 | +10.2±14.5 | 0.0001 |
| Night-time SBP, mmHg | 115.8±14.6 | 122.9±16.8 | +7.0±16.4 | 0.008 |
| Mean 24-hour DBP, mmHg | 69.1±8.2 | 73.1±9.2 | +3.2±6.9 | 0.002 |
| Mean 24-hour heart rate. bpm | 70.5±11.2 | 68.7±9.2 | -1.8±10.0 | 0.24 |
| Daytime SBP drop <90 mmHg | | | | |
| - Total number | 75 | 33 | -56% | |
| - Median number (IQR) | 1 (0;2) | 0 (0;1) | -1 (0 to -3) | 0.031 |
| 24-hour SBP drops <90 mmHg | | | | |
| - Total number | 112 | 51 | -64% | |
| - Median number (IQR) | 2 (0 to 3) | 0 (0 to 1) | -1 (-2 to 0) | 0.006 |
| Daytime SBP drop <100 mmHg: | | | | |
| - Total number | 251 | 89 | -65% | |
| - Median number (IQR) | 4 (1 to 7) | 1 (0 to2) | -2 (-5 to -1) | <0.0001 |
| 24-hour SBP drops <100 mmHg | | | | |
| - Total number | 369 | 142 | -62% | |
| - Median number (IQR) | 6 (3 to 13) | 2 (0 to 5) | -4 (-10.5 to -1) | <0.0001 |

**Supplementary Table S4.** ABPM results in 67 patients assigned to BP rising drugs according to the Intention-to-treat principle.

| | ABPM 1 | ABPM 2 | Difference | P value |
|---|---|---|---|---|
| Mean 24-hour SBP, mmHg | 110.1±11.2 | 116.4±12.6 | +6.3±8.8 | <0.0001 |
| Daytime SBP, mmHg | 112.1±10.2 | 118.9±11.5 | +6.8±9.3 | <0.0001 |
| Night-time SBP, mmHg | 102 (96 to 109) | 106 (96 to 119) | +3.5 (-2 to 11) | 0.0004 |
| Mean 24-hour DBP, mmHg | 68.5±7.0 | 71.2±6.9 | +2.7±6.2 | 0.0006 |
| Mean 24-hour heart rate. bpm | 73.9±12.6 | 71.6±10.6 | -1.0±11.4 | 0.12 |
| Daytime SBP drop <90 mmHg | | | | |
| - Total number | 219 | 83 | -62% | |
| - Median number (IQR) | 2 (1 to 4) | 0 (0 to 1) | - 2 (-1 to -5) | <0.0001 |
| 24-hour SBP drops <90 mmHg | | | | |
| - Total number | 429 | 243 | -43% | |
| - Median number (IQR) | 4 (2 to 10) | 1 (0 to 6) | -2 (-4 to 0) | <0.0001 |
| Daytime SBP drop <100 mmHg: | | | | |
| - Total number | 619 | 365 | -41% | |
| - Median number (IQR) | 7 (4 to12) | 3 (1 to7) | -3 (-7.5 to -1) | <0.0001 |
| 24-hour SBP drops <100 mmHg | | | | |
| - Total number | 1078 | 771 | -28% | |
| - Median number (IQR) | 15 (7 to 22) | 9 (3 to 17) | -4 (-9 to 0) | 0.007 |

**Supplementary Table S5.** Changes in the number of SBP drops stratified according to the median age of the study population between ABPM 1 and ABPM 2

| | ABPM 1 | ABPM 2 | Difference | P value |
|---|---|---|---|---|
| ≥58 years (56 patients) | | | | |
| Mean 24-hour SBP*, mmHg* | 119.1±10.6 | 129.2±13.4 | 10 (2 to 17) * | 0.0005 |
| Daytime SBP drop <90 mmHg | | | | |
| - Total number | 162 | 77 | -52% | |
| - Median number (IQR) | 1.5 (0 to 3) | 0 (0 to1) | -1 (-2 to 0) ** | 0.0012 |
| 24-hour SBP drops <90 mmHg | | | | |
| - Total number | 217 | 104 | -52% | |
| - Median number (IQR) | 2 (1 to 5) | 0.5 (0 to 2) | -2.5 (-8 to -1) † | <0.0001 |
| Daytime SBP drop <100 mmHg | | | | |
| - Total number | 425 | 175 | -59% | |
| - Median number (IQR) | 5 (2 to 10) | 1 (0 to 4) | -2.5 (-8 to -1) ‡ | <0.0001 |
| 24-hour SBP drops <100 mmHg | | | | |
| - Total number | 580 | 243 | -58% | |
| - Median number (IQR) | 7 (4 to 15) | 2 (1 to 7) | -4.5 (-12 to -1) # | <0.0001 |
| <58 years (55 patients) | | | | |
| Mean 24-hour SBP, mmHg | 109.1±11.4 | 113.5±10.9 | 3 (0 to 8.5) * | 0.0005 |
| Daytime SBP drop <90 mmHg | | | | |
| - Total number | 132 | 39 | -70% | |
| - Median number (IQR) | 1 (1 to 3) | 0 (0 to 1) | -1 (-2 to .1) ** | <0.0001 |
| 24-hour SBP drops <90 mmHg | | | | |
| - Total number | 324 | 190 | -41% | |
| - Median number (IQR) | 4 (2 to 7) | 1 (0 to 5) | -2 (-4 to 0) † | 0.0002 |
| Daytime SBP drop <100 mmHg | | | | |
| - Total number | 445 | 279 | -37% | |
| - Median number (IQR) | 7 (2 to 11) | 3 (0 to 7) | -3 (-7 to -1) ‡ | <0.0001 |
| 24-hour SBP drops <100 mmHg | | | | |
| - Total number | 867 | 670 | -23% | |
| - Median number (IQR) | 14 (6 to 22) | 10 (3 to 17) | -2 (-8 to 0) # | <0.0001 |

Comparison between the two subgroups: *P<0.004; **P=0.13; †P=0.43; ‡P<0.0006; #P<0.082

**Supplementary Table S6.** Changes in the number of SBP drops stratified according to the median of the differences of 24-hour SBP between ABPM 1 and ABPM 2

| | ABPM 1 | ABPM 2 | Difference | P value |
|---|---|---|---|---|
| Difference of 24h SBP >median (57 patients) | | | | |
| Mean 24-hour SBP*, mmHg* | 112.8±10.0 | 128.4±13.0 | 13 (10 to 20) * | <0.0001 |
| Daytime SBP drop <90 mmHg | | | | |
| - Total number | 188 | 51 | -73% | |
| - Median number (IQR) | 2 (1 to 4) | 0 (0 to1) | -1 (-3 to 0) ** | <0.0001 |
| 24-hour SBP drops <90 mmHg | | | | |
| - Total number | 296 | 87 | -71% | |
| - Median number (IQR) | 3 (2 to 5) | 1 (0 to 3) | -2 (-4 to -1) † | <0.0001 |
| Daytime SBP drop <100 mmHg | | | | |
| - Total number | 527 | 146 | -72% | |
| - Median number (IQR) | 7 (4 to 12) | 1 (0 to 3) | -5 (-10 to -2) ‡ | <0.0001 |
| 24-hour SBP drops <100 mmHg | | | | |
| - Total number | 810 | 270 | -64% | |
| - Median number (IQR) | 14 (6 to 19) | 1 (0 to 2) | -8 (-13 to -4) # | <0.0001 |
| Difference of 24h SBP <median (54 patients) | | | | |
| Mean 24-hour SBP, mmHg | 115.6±13.9 | 114.1±12.2 | 1 (-4 to +3) * | 0.69 |
| Daytime SBP drop <90 mmHg | | | | |
| - Total number | 106 | 65 | -39% | |
| - Median number (IQR) | 1 (1 to 2) | 0 (0 to 0) | -1 (-2 to 0) ** | 0.0043 |
| 24-hour SBP drops <90 mmHg | | | | |
| - Total number | 245 | 207 | -26% | |
| - Median number (IQR) | 2.5 (1 to 7) | 2.5 (1 to 7) | -0.5 (-2 to +1) † | 0.072 |
| Daytime SBP drop <100 mmHg | | | | |
| - Total number | 343 | 308 | -10% | |
| - Median number (IQR) | 4 (2 to 9) | 2 (0 to 3) | -1 (-3 to +1) ‡ | 0.057 |
| 24-hour SBP drops <100 mmHg | | | | |
| - Total number | 637 | 643 | +1% | |
| - Median number (IQR) | 8.5 (4 to 17) | 5 (1 to 9) | 0 (-3 to +3) # | 0.70 |

Comparison between the two subgroups: *P<0.0001; **P=0.010; †P=0.0007; ‡P<0.0001; #P<0.0001

**Supplementary figure 1**. Effect of therapy on symptoms reported between ABPM 1 and ABPM 2 in the overall sample (n=111) and in the Deprescription (n=44) and Vasoactive (n=66) groups (one patient in the vasoactive group was missing). Intention-to-treat analysis.