CHAPTER 8

Haemodynamic effects of fludrocortisone and midodrine in patients with symptoms due to hypotension

Frederik J. de Lange, Steven van Zanten, Giulia Rivasi, Antonella Groppelli, Vincenzo Russo, Roberto Maggi, Marco Capacci, Sara Nawaz, Angelo Comune, Andrea Ungar, Gianfranco Parati, Michele Brignole, Artur Fedorowski

Clinical Autonomic Research 35, 523–527 (2025)

doi.org/10.1007/s10286-024-01096-3

INTRODUCTION

The hypotensive phenotype is characterized by hypotensive susceptibility as the predominant hemodynamic mechanism responsible for reflex syncope, presyncope and other symptoms due to orthostatic intolerance.[1] Hypotensive phenotype is common in patients with persistent hypotension, the so-called constitutional hypotension[2] and in patients with intermittent low blood pressure (BP), i.e. hypotensive episodes observed in individuals with mean BP values within the normal/low range.[1,3,4] A recent study (SynABPM1)[5] demonstrated that reflex syncope patients more frequently show daytime, and 24-hour SBP drops on 24-hour ambulatory blood pressure monitoring (ABPM) compared with non-syncopal individuals. Daytime episodes of SBP <90 mmHg (at least one) and <100 mmHg (at least two) were identified as the susceptibility markers which best discriminated patients with reflex syncope from controls, independently of the presence of symptoms. SBP drops on ABPM can represent manifestations of hypotensive susceptibility, i.e., a predisposition to (symptomatic) hypotensive episodes and may contribute to identification of patients with the so-called hypotensive phenotype of reflex syncope. This also underscores the important clinical application of the 24-hour ABPM in the syncope unit.[6,7] A subsequent proof-of-concept study (SynABPM2) showed that interventions aimed to increase average BP values reduced the number of SBP drops and, potentially, prevented syncopal recurrences and improved symptoms of orthostatic intolerance.[8] A more recent study [9] showed that a mean 24-hour systolic BP (SBP) ≤110 mmHg on ABPM can predict a diagnosis of reflex syncope.

The present study is an efficacy and exploratory subgroup analysis of the SynABPM2 study[8] aimed to assess the hemodynamic effects (i.e., average BP increase and reduction of SBP drops) of fludrocortisone and midodrine, alone or combined, in patients with recurrent syncope and/or symptoms due to hypotension.

METHOD

This multicentre, observational proof-of-efficacy study was performed in patients with reflex syncope and/or other symptoms due to hypotension and SBP drops on ABPM (ABPM1), who were treated with fludrocortisone and/or midodrine to increase the average BP, reduce/abolish SBP drops and prevent symptom recurrences. Eligible patients underwent a second ABPM (ABPM2) within 6 months of the first ABPM and the results of the two ABPMs were compared to assess the effects of BP-elevating therapy (**Figure 1**). The study was approved by the Ethical Committees of the participating centres and informed consent was obtained.

Figure 1

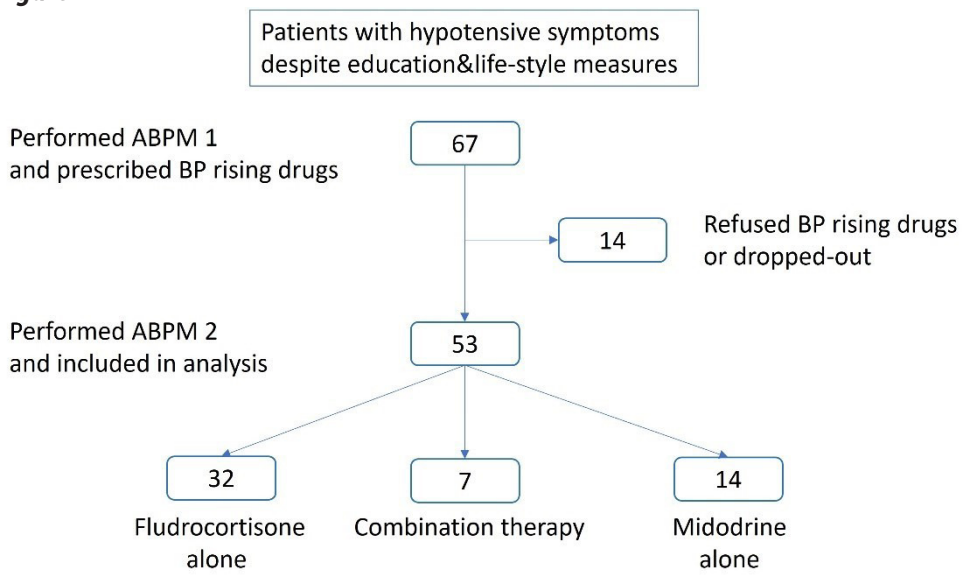


Figure 1. The flow of study participants. Fourteen patients of 67 did not complete the pharmacological intervention (either with midodrine or fludrocortisone or both). ABPM: Ambulatory Blood Pressure Monitoring; BP: Blood Pressure; DBP: Diastolic Blood Pressure.

Inclusion criteria

Patients who met the following criteria were included in the study:

1. Established diagnosis of reflex syncope and/or symptoms of hypotension which persisted despite education and lifestyle measures.
2. ≥1 daytime SBP drop <90 mmHg or ≥2 daytime SBP drops <100 mmHg recorded by ABPM performed during the routine work-up of syncope.[5]
3. Treatment with fludrocortisone or midodrine, alone or combined.

In complying with European Society of Cardiology (ESC) syncope guidelines[10], reflex syncope was diagnosed when clinical history was 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. Symptoms of hypotension included presyncope or minor symptoms (e.g., dizziness, lightheadedness, orthostatic intolerance). Persistent hypotension was defined as mean 24-hour systolic SBP ≤110 mmHg.[9]

Exclusion criteria

1. Age <18 years
2. Symptomatic orthostatic hypotension, defined as a symptomatic fall in SBP ≥20 mm Hg and/or a SBP decrease to <90 mmHg within 3 min of standing, according to the diagnostic criteria of the ESC guidelines[10]
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[10]

4. Severe cardiac disease, previous stroke or transient ischaemic attack

Study objectives (endpoints)

The effect of interventions (pharmacological and non-pharmacological) on increasing arterial blood pressure and reducing SBP drops.

Study medications

Fludrocortisone and midodrine were administered empirically according to the investigators clinical judgement and were titrated with the final purpose to achieve symptom control. ABPM 2 was performed once the prescribed therapy was deemed stable. Practical use of fludrocortisone and/or midodrine entails the following: the initial dosage of fludrocortisone is 0,1 mg daily. This could be increased to 0,2 mg daily based on investigators clinical judgement. The initial dosage of midodrine is 2,5 mg three times daily. This could be increased to a usual maintenance dosage of 10 mg three times daily based on investigators clinical judgement. Additionally, this medication should not be taken four hours before bedtime to prevent supine hypertension.

Contraindications for the use of fludrocortisone and/or midodrine are:

Severe organic cardiac conditions (e.g., bradycardia, ischemic heart disease, heart failure, cardiac conduction disorders, aortic aneurysm)

- Severe occlusive vascular diseases, cerebrovascular occlusions, and vasospasms
- Acute renal insufficiency, severe renal insufficiency (creatinine clearance <30ml/min)
- Prostate hyperplasia
- Urinary retention
- Proliferative diabetic retinopathy
- Narrow-angle glaucoma
- Hyperthyroidism
- Hypertension
- Pheochromocytoma

Study outcome measures

The following data were collected and compared between ABPM 1 and ABPM2:

- Average 24-hour SBP, diastolic BP and heart rate
- Average daytime and night-time SBP
- Number of daytime SBP drops <90 mmHg
- Number of 24-hour SBP drops <90 mmHg
- Number of daytime SBP drops <100 mmHg
- Number of 24-hour SBP drops <100 mmHg

SBP drops consisted of SBP measures <100 or <90 mmHg.[5] Taking into consideration possible differences in actual sleep time, daytime was defined as the period between 07:00 am and 11:00 pm. At the time of ABPM 2, patients were asked to rank their quality of life and symptom control by mean of a 4-item semi-

quantitative scale, in comparison with ABPM 1.

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 showed as absolute and relative frequencies. Pre-post comparisons of continuous variables were performed by means of the t-test paired or Wilcoxon ranked-signed test, as appropriate. Comparison of proportion was performed by means of Fisher exact test. All tests were two-sided and p-values less than 0.05 were considered statistically significant. Analyses were conducted using MedCalc, version 15.8 (Med Calc Software, Mariakerke, Belgium).

RESULTS

Characteristics of the study sample

There were 67 eligible patients. Of these, 14 patients were excluded because they refused treatment with BP-elevating drugs or dropped-out before ABPM2. Thus, the study sample included 53 patients: 32 were treated with fludrocortisone, 14 with midodrine and 7 with both drugs (**Figure 1**). The clinical characteristics of the study sample are reported in the **Table 1**.

24-hour SBP recorded on ABPM1 was lower in patients assigned to fludrocortisone than in those assigned to midodrine, p=0.04 (**Tables 2 and 3**). The median number of daytime drops <90 and <100 mmHg was similar in the two groups, but the median number during 24-hour monitoring was significantly higher in patients assigned to fludrocortisone (p=0.047 and p=0.0003 for SBP drops <90 and <100 mmHg, respectively). Fludrocortisone was prescribed at increasing doses with the average dose of 0.2 mg per day. Midodrine was prescribed 2.5 mg to 10 mg two or three times per day, with an average dose of 2.5 mg three times per day. The median time interval between ABPM1 and ABPM2 was 3.3 months (interquartile range, 2.0; 5.7).

Comparison between ABPM 1 and ABPM 2

The changes in average BP values and SBP drops between ABPM 1 and ABPM 2 are reported in the **Table 2, 3 and 4,** respectively, and in **Figure 2**.

24-hour SBP increased in all the study groups, with a greater increase in patients receiving fludrocortisone as compared to those receiving midodrine. The number of SBP drops decreased significantly in both drugs, with a more pronounced decrease in patients treated with fludrocortisone.

During the study period, both treatments were well tolerated and no side effects were recorded. At the time of ABPM 2, the proportion of participants reporting substantial or at least moderate symptom improvement was 69% with fludrocortisone, 71% with midodrine and 86% with the combination therapy **(Figure 3**).

Table 1. Characteristics of the study sample. SBP: Systolic Blood Pressure.

	Total population n=53	Fludrocortisone n=32	Midodrine n=14	Fludrocortisone + midodrine n=7
Mean age, yrs ±SD	40.9±18.5	40.2±19.92	44.4±17.5	37.1±15.0
Females	37 (70%)	21 (66%)	11 (79%)	5 (71%)
History of syncope:	46 (87%)	22 (69%)	10 (71%)	
- Total number during life, (IQR)	10 (7;10)	10 (10;10)	10 (2;17)	10 (7;17)
- Syncopes/last year, (IQR)	4 (2;5)	4 (3;5)	5 (2;10)	2 (2;3)
Presyncopes and hypotensive symptoms	42 (79%)	25 (78%)	10 (71%)	7 (100%)
Triggers (%):				
- Orthostatic	44 (83%)	27 (84%)	11 (79%)	5 (71%)
- Emotional	3 (6%)	1 (3%)	2 (14%)	0
- Situational	1 (2%)	2 (6%)	0 (0%)	1 (14%)
- Undetermined	5 (9%)	2 (6%)	1 (7%)	1 (14%)
ECG abnormalities	10 (19%)	5 (16%)	4 (29%)	1 (14%)
Structural heart disease	4 (8%)	3 (9%)	0 (0%)	1 (14%)
Office SBP, mmHg	116.8±15.9	116.2±17.1	120.7±13.3	112.0±14.8
Persistent hypotension	34 (64%)	24 (75%)	5 (36%)	5 (71%)
Tilt testing	30	15	10	5
- Positive, mixed form	15 (50%)	11 (73%)	4 (29%)	0 (86%)
- Positive, cardioinhibitory form	4 (13%)	1 (7%)	1 (7%)	1 (14%)
Carotid sinus massage	14	11	3	2
- Positive (%)	1 (2%)	1 (8%)	0 (0%)	0 (100%)

Table 2. Results in 32 patients assigned to Fludrocortisone.

	ABPM 1	ABPM 2	Difference	P value
Mean 24-hour SBP, mmHg ±SD	107.1±9.9	116.3±14.9	+9.2±9.2	<0.0001
Daytime SBP, mmHg ±SD	109.1±8.7	119.0±13.3	+9.9±9.8	<0.0001
Nighttime SBP, mmHg ±SD	102.2±14.0	109.9±21.2	+8.7±11.8	0.0003
Mean 24-hour DBP, mmHg ±SD	67.8±6.8	72.7±8.1	+4.8±5.9	<0.0001
Mean 24-hour heart rate, bpm ±SD	72.1±11.6	71.6±11.3	-0.5±6.4	0.68
Daytime SBP drops <90 mmHg				
- Total number	126	34	-73%	
- Median number (IQR)	2 (1;5)	0 (0;1)	-1.5 (-3;-1)	<0.0001
24-hour SBP drops <90 mmHg				
- Total number	232	117	-50%	
- Median number (IQR)	5 (2;11)	1 (0;6)	-3 (-6;-1)	0.0005
Daytime SBP drops <100 mmHg:				
- Total number	346	203	-41%	
- Median number (IQR)	9 (4;16)	3 (0;9)	-5 (-9;-2)	0.0019
24-hour SBP drops <100 mmHg				
- Total number	572	381	-33%	
- Median number (IQR)	16 (10;24)	11 (1;16)	-5 (-10;0)	<0.0001

Efficacy analysis. The mean time interval between ABPM1 and ABPM2 was 3.3 months (interquartile range 2.0; 5.7). ABPM: Ambulatory Blood Pressure Monitoring; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure, SD: Standard Deviation.

Table 3. Results in 14 patients assigned to Midodrine.

	ABPM 1	ABPM 2	Difference	P value
Mean 24-hour SBP, mmHg ±SD	112.7±7.4	115.0±9.1	+2.3±5.1	0.12
Daytime SBP, mmHg ±SD	115.0±6.9	116.6±8.7	+1.7±5.8	0.30
Nighttime SBP, mmHg ±SD	106.4±10.2	107.4±11.1	+1.0±6.5	0.57
Mean 24-hour DBP, mmHg ±SD	70.2±7.5	68.2±6.0	-2.0±6.4	0.26
Mean 24-hour heart rate. bpm ±SD	78.8±12.8	71.8±9.7	-7.0±13.3	0.079
Daytime SBP drops <90 mmHg				
- Total number	29	14	-52%	
- Median number (IQR)	2 (1;2)	0 (0;2)	-1 (-2;-0)	0.042
24-hour SBP drops <90 mmHg				
- Total number	46	39	-15%	
- Median number (IQR)	2 (1;6)	1.5 (1;4)	-0.5 (-2;1)	0.79
Daytime SBP drops <100 mmHg:				
- Total number	88	56	-36%	
- Median number (IQR)	6 (4;9)	3 (3;5)	-2 (-3;-1)	0.0007
24-hour SBP drops <100 mmHg				
- Total number	167	120	-28%	
- Median number (IQR)	12 (6;15)	5.5 (3;14)	-2 (-8;0)	0.034

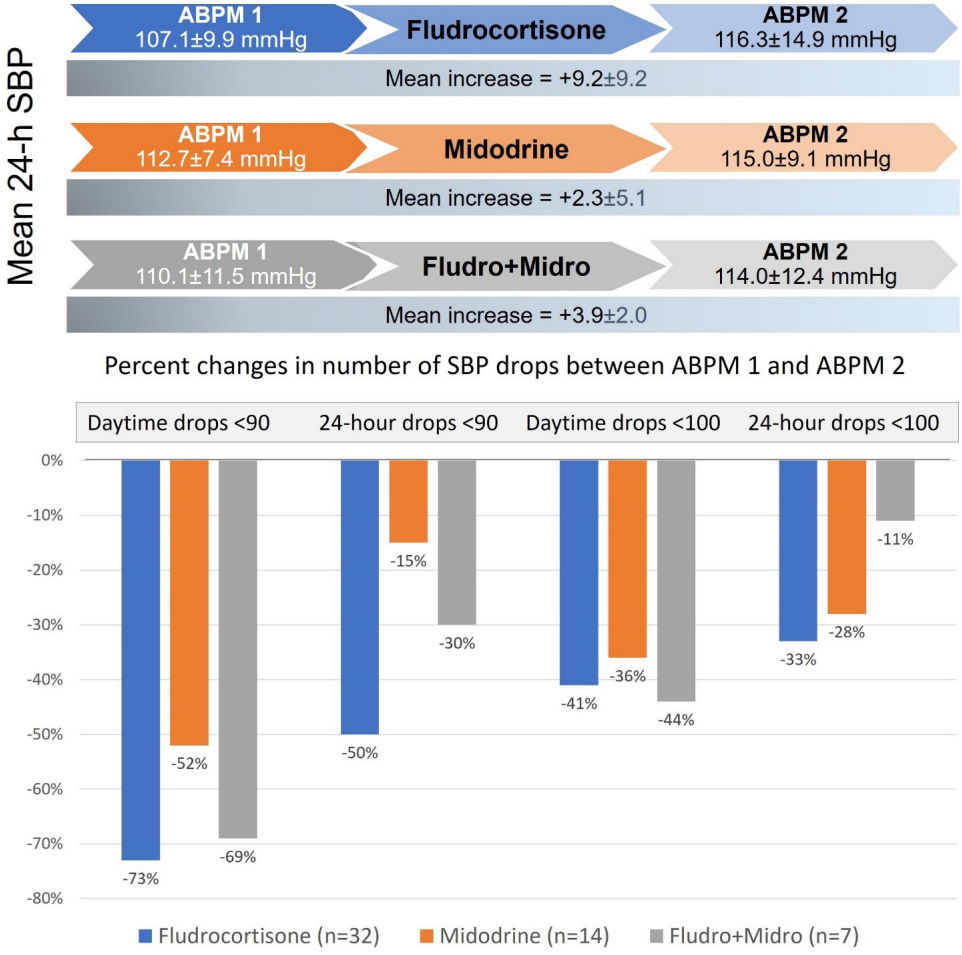
Efficacy analysis. ABPM: Ambulatory Blood Pressure Monitoring; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure, SD: Standard Deviation.

Table 4. Results in 7 patients assigned to fludrocortisone plus midodrine.

	ABPM 1	ABPM 2	Difference	P value
Mean 24-hour SBP, mmHg ±SD	110.1±11.5	114.0±12.4	+3.9±2.0	0.002
Daytime SBP, mmHg ±SD	112.3±9.6	117.6±10.2	+5.3±2.4	0.001
Nighttime SBP, mmHg ±SD	103.6±19.0	105.3±18.6	+1.7±2.8	0.16
Mean 24-hour DBP, mmHg ±SD	68.4±4.1	71.3±4.7	+2.9±3.0	0.04
Mean 24-hour heart rate. bpm ±SD	70.0±11.5	70.6±12.0	+0.6±6.5	0.82
Daytime SBP drops <90 mmHg				
- Total number	13	4	-69%	
- Median number (IQR)	1 (1;3)	0.5 (0;1)	-0.5(-3;+1)	0.22
24-hour SBP drops <90 mmHg				
- Total number	44	31	-30%	
- Median number (IQR)	4 (3;9)	2 (2;8)	-2 (-3;-1)	0.44
Daytime SBP drops <100 mmHg:				
- Total number	63	35	-44%	
- Median number (IQR)	10 (5;14)	5 (3;7)	-3 (-6;-2)	0.04
24-hour SBP drops <100 mmHg				
- Total number	122	108	-11%	
- Median number (IQR)	21 (8;27)	10 (6;26)	-2 (-6;+2)	0.85

Efficacy analysis. ABPM: Ambulatory Blood Pressure Monitoring; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure, SD: Standard Deviation.

Figure 2



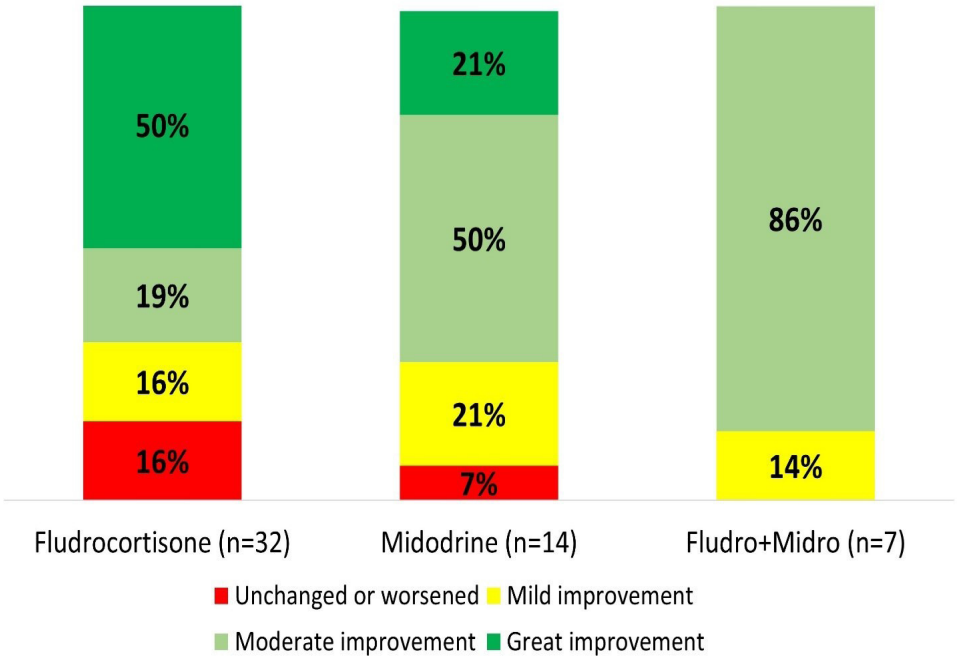
Effect of vasoactive therapy on SBP drops between ABPM 1 and ABPM 2. ABPM: Ambulatory Blood Pressure Monitoring; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

During the study period, syncope recurred in four patients, of whom three were receiving fludrocortisone and one midodrine. All these patients showed a minimal increase of 24-hour SBP (from 101.8±2.2 mmHg during ABPM1 to 105.3±1.0 mmHg during ABPM2) and persistence of 24-hour SBP drops <90 mmHg (totally, nine at both measurements) and slight decrease in SBP drops<100 mmHg (totally, from 39 to 33).

DISCUSSION

We observed that both fludrocortisone and midodrine effectively increase 24-hour SBP and reduce number of SBP drops in patients with reflex syncope and/or symptoms related to hypotension. This proof-of-efficacy study supports the results of the earlier clinical randomized controlled trials performed with

Figure 3. Effect of BP-rising drugs on patients symptoms and quality of life between ABPM 1 and ABPM 2.



fludrocortisone[11] and midodrine[12,13] and provides a physiological explanation of their possible efficacy in preventing syncopal recurrences. Recent studies showed that individuals with reflex syncope have a different hemodynamic profile compared with the general population, due to lower SBP, higher diastolic BP and heart rate.[14] The findings of lower 24-hour SBP and more frequent SBP drops on ABPM in patients with syncope support the hypothesis of hypotensive phenotype and hypotensive susceptibility as important components of reflex syncope.[5,9] The presence of baseline hypotensive susceptibility implies that syncope and other symptoms of hypotension may occur in the presence of triggering conditions such as prolonged standing, that overcome the capacity of compensatory mechanisms, resulting in BP fall, cerebral hypoperfusion, and syncope.[15] By increasing average BP, fludrocortisone and midodrine can prevent the development of the reflex cascade and make symptoms of hypotension less common or intolerance less severe in patients with hypotensive phenotype.

In the literature, the haemodynamic effects of fludrocortisone and midodrine have not been previously assessed by 24hABPM. Also, little is known about the haemodynamic effects of these drugs in patients with reflex syncope. The mineralocorticoid fludrocortisone expands intravascular volume by increasing renal water and sodium reabsorption. In a systematic review of patients with neurogenic orthostatic hypotension, there was very weak evidence that fludrocortisone improves standing BP.[16] Midodrine, a peripheral alpha1-adrenoreceptor agonist, was found to increase BP in patients with syncope undergoing tilt testing.[17-19] The ability of fludrocortisone and midodrine to reduce

SBP drops shown in the present study is thus original and explanatory for their postulated antihypotensive and symptom-reducing mechanism.

A comparison of efficacy between fludrocortisone and midodrine was outside the scope of the present study and patients assigned to the two treatment groups were different. However, some observations can be considered. The patients assigned to fludrocortisone had lower 24-hour SBP and a greater number of 24-hour SBP drops during ABPM1, while showing a greater increase of 24-hour SBP and a greater reduction of SBP drops. A 24-hour SBP value of 115 mmHg and/or a 10 mmHg increase in 24-hour SBP might represent reasonable targets in patients receiving fludrocortisone, allowing to safely achieve decrease in both daily SBP drops <90 mmHg and <100 mmHg by 73% and 41%, respectively.

Fludrocortisone seems to have a more pronounced effect than midodrine on increase in 24-hour SBP and reduction of SBP drops. The plasma level of midodrine peaks after about half an hour, while its active metabolite reaches peak blood concentrations after about 1 to 2 hours and has a half-life of approximately 3 to 4 hours. Consequently, the shorter effect duration of midodrine may likely explain the lower increase in 24-hour SBP. The subgroup of patients taking both fludrocortisone and midodrine were probably the most difficult to treat. An individual personalized approach using careful combination of the two drugs is required to achieve the therapeutic goal.

The study was not designed to assess the effect of the two drugs on symptoms and syncope recurrence. Well performed randomized controlled trials and meta-analyses have already proven their clinical efficacy.[11-13] However, the four patients who had syncope recurrence during the 6-month study period had a minimal increase of 24-hour SBP during ABPM2 and persistence of daily SBP drops, thus indirectly confirming the need of increasing 24-hour SBP and reducing SBP drops in order to prevent syncopal recurrences. During the study period, treatments were well tolerated without side effects and approximately two third of patients reported moderate or great satisfaction compared to the period before treatment. However, clinical benefits should be addressed by a blinded randomized control trial.

Limitations

The study sample involves individuals of young age, therefore these data are to a limit extend applicable in older patients. The follow up of the study was too short to investigate long term changes in cardiovascular risk associated with 24-hour SBP increase and thus we are not able to draw conclusions on safety issues. Data on compliance to medication use is missing which might at least partly explain the differences in the effect of midodrine and fludrocortisone. Due to its design with a short follow-up period, the present study was could not be aimed at exploring the impact of SBP drops reduction on actual syncope recurrences. In conclusion the findings of this exploratory study and the actual possibility to prevent recurrent syncope through prescription of blood pressure-rising drugs need to be further addressed in in the setting of a prospective randomized controlled clinical trial.

CONCLUSION AND PERSPECTIVES

In patients with hypotensive susceptibility on SBP drops on ABPM, treatment with either fludrocortisone or midodrine was able to increase 24-hour SBP and decrease daily SBP drops. This data paves the way to future randomized intervention trials that might test the actual ability of fludrocortisone and midodrine to prevent syncope recurrence in patients with presumed hypotensive phenotype.

ACKNOWLEDGEMENT
None

SOURCES OF FUNDING
Partial financial support was received from the Italian Ministry of Health.

NOTHING TO DECLARE
All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

DISCLOSURES
The authors declare no competing interests.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

APPROVAL ID NUMBER OF THE ETHICS COMMITTEE THAT APPROVED THIS STUDY
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the appropriate institutional committees. The approval ID number of the Ethics committee is: 2022_09_27_16

PATIENTS AND PUBLIC INVOLVEMENT
Patients gave their informed consent prior before inclusion in this study. Patients were actively involved in the follow up, quality of life analysis and the tolerance of the prescribed blood pressure-rising drugs of this study.

REFERENCES

1. Brignole M, Rivasi G. (2021) New insights in diagnostics and therapies in syncope: a novel approach to non-cardiac syncope. Heart.107(11):864-73. https://doi.org/10.1136/heartjnl-2020-318261
2. Duschek S, Schandry R. (2007) Reduced brain perfusion and cognitive performance due to constitutional hypotension. Clin Auton Res.17(2):69-76. https://doi.org/10.1007/s10286-006-0379-7
3. de Jong JSY, Blok MRS, Thijs RD, Harms MPM, Hemels MEW, de Groot JR, et al. (2021) Diagnostic yield and accuracy in a tertiary referral syncope unit validating the ESC guideline on syncope: a prospective cohort study. Europace.23(5):797-805. https://doi.org/10.1093/europace/euaa345
4. de Jong JSY, van Zanten S, Thijs RD, van Rossum IA, Harms MPM, de Groot JR, et al. (2023) Syncope Diagnosis at Referral to a Tertiary Syncope Unit: An in-Depth Analysis of the FAST II. J Clin Med.12(7). https://doi.org/10.3390/jcm12072562
5. Rivasi G, Groppelli A, Brignole M, Soranna D, Zambon A, Bilo G, et al. (2022) Association between hypotension during 24 h ambulatory blood pressure monitoring and reflex syncope: the SynABPM 1 study. Eur Heart J.43(38):3765-76. https://doi.org/10.1093/eurheartj/ehac347
6. van Zanten S, Sutton R, Hamrefors V, Fedorowski A, de Lange FJ. (2023) Tilt table testing, methodology and practical insights for the clinic. Clin Physiol Funct Imaging. https://doi.org/10.1111/cpf.12859
7. van Zanten S, de Jong JSY, Scheffer MG, Kaal ECA, de Groot JR, de Lange FJ. (2023) A cross-sectional nationwide survey of guideline based syncope units in the Netherlands: the SU-19 score-a novel validation for best practices. Europace.26(1). https://doi.org/10.1093/europace/euae002
8. Groppelli A, Rivasi G, Fedorowski A, de Lange F, Russo V, Maggi R, et al. (2024) Interventions aimed to increase average 24-hour systolic blood pressure reduce blood pressure drops in patients with reflex syncope and orthostatic intolerance. Europace. https://doi.org/10.1093/europace/euae026
9. Sharad B, Rivasi G, Hamrefors V, Johansson M, Ungar A, Sutton R, et al. (2023) Twenty-Four-Hour Ambulatory Blood Pressure Profile in Patients With Reflex Syncope and Matched Controls. J Am Heart Assoc.12(8):e028704. https://doi.org/10.1161/JAHA.122.028704
10. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, et al. (2018) 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J.39(21):1883-948. https://doi.org/10.1093/eurheartj/ehy037
11. Sheldon R, Raj SR, Rose MS, Morillo CA, Krahn AD, Medina E, et al. (2016) Fludrocortisone for the Prevention of Vasovagal Syncope: A Randomized, Placebo-Controlled Trial. J Am Coll Cardiol.68(1):1-9. https://doi.org/10.1016/j.jacc.2016.04.030

12. Sheldon R, Faris P, Tang A, Ayala-Paredes F, Guzman J, Marquez M, et al. (2021) Midodrine for the Prevention of Vasovagal Syncope : A Randomized Clinical Trial. Ann Intern Med.174(10):1349-56. https://doi.org/10.7326/M20-5415

13. Lei LY, Raj SR, Sheldon RS. (2022) Midodrine for the prevention of vasovagal syncope: a systematic review and meta-analysis. Europace.24(7):1171-8. https://doi.org/10.1093/europace/euab323

14. Brignole M, Rivasi G, Sutton R, Kenny RA, Morillo CA, Sheldon R, et al. (2021) Low-blood pressure phenotype underpins the tendency to reflex syncope. J Hypertens.39(7):1319-25. https://doi.org/10.1097/HJH.0000000000002800

15. Sutton R, Brignole M. (2014) Twenty-eight years of research permit reinterpretation of tilt-testing: hypotensive susceptibility rather than diagnosis. Eur Heart J.35(33):2211-2. https://doi.org/10.1093/eurheartj/ehu255

16. Veazie S, Peterson K, Ansari Y, Chung KA, Gibbons CH, Raj SR, et al. (2021) Fludrocortisone for orthostatic hypotension. Cochrane Database Syst Rev.5(5):CD012868. https://doi.org/10.1002/14651858.CD012868.pub2

17. Ward CR, Gray JC, Gilroy JJ, Kenny RA. (1998) Midodrine: a role in the management of neurocardiogenic syncope. Heart.79(1):45-9. https://doi.org/10.1136/hrt.79.1.45

18. Kaufmann H, Saadia D, Voustianiouk A. (2002) Midodrine in neurally mediated syncope: a double-blind, randomized, crossover study. Ann Neurol.52(3):342-5. https://doi.org/10.1002/ana.10293

19. Behnoush AH, Yazdani K, Khalaji A, Tavolinejad H, Aminorroaya A, Jalali A, et al. (2023) Pharmacologic prevention of recurrent vasovagal syncope: A systematic review and network meta-analysis of randomized controlled trials. Heart Rhythm.20(3):448-60. https://doi.org/10.1016/j.hrthm.2022.12.010