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ORIGINAL ARTICLE

Stop vasodepressor drugs in reflex syncope: a randomised controlled trial

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ABSTRACT

Objectives Most elderly patients affected by reflex vasodepressor syncope take one or more hypotensive drugs. The role of these drugs in causing syncope has not yet been established. We hypothesised that recurrence of syncope and presyncope can be reduced by discontinuing/reducing vasoactive therapy without increasing the risk of cardiovascular and neurological events.

Methods This randomised, parallel, prospective, trial was conducted from January 2014 to March 2016 in four general hospitals. Of 328 initially screened participants, 58 patients (mean (SD) age 74±11 years) affected by vasodepressor reflex syncope, which was reproduced by tilt testing (n=54) or carotid sinus massage (n=4), were randomised to stop/reduce vasoactive therapy or to continue it. Primary end point was recurrence of syncope, presyncope or adverse events (defined as stroke, cerebral transient ischaemic attacks, worsening heart failure, myocardial infarction).

Results Of 58 patients who were randomised, 55 completed the trial. After 1 month, systolic blood pressure was significantly higher in the 'stop/reduce' group than in the 'continue' group, in both supine (141 ±13 mm Hg vs 128±14 mm Hg; p=0.004) and standing (133±13 mm Hg vs 122±15 mm Hg; p=0.02) positions. During a mean follow-up of 13±7 months, the primary combined end point occurred in seven 'stop/reduce' patients (23%): three had syncope, three had presyncope and one had heart failure. Conversely, it occurred in 13 'continue' patients (54%): 10 had syncope, 2 had presyncope and 1 had cerebral transient ischaemic attack. The log-rank p value was 0.02 and the HR was 0.37 (95% CI 0.15 to 0.91).

Conclusions Recurrence of syncope and presyncope can be reduced by discontinuing/reducing vasoactive therapy in most elderly patients affected by reflex vasodepressor syncope.

Trial registration number NCT01509534; EudraCT2013-004364-63; Results.

INTRODUCTION

Many elderly patients affected by reflex vasodepressor syncope take one or more hypotensive drugs for associated conditions. For example, in the Syncope Unit Project Two study,[1] 61% of the elderly patients affected by reflex syncope (mean age of 70 years) were taking vasoactive therapy. Although it is generally believed that vasoactive drugs may have a role in causing vasodepressor reflex syncope, no study has yet evaluated the long-term effects of discontinuation or reduction of such therapies. In the absence of the evidence from trials of a direct cause-effect relationship between vasoactive drugs and syncope, physicians are reluctant to discontinue or reduce vasoactive drugs because they are concerned about worsening of the underlying diseases for which such therapies had been prescribed and about the risk of cardiovascular events caused by high blood pressure (BP) values. In the era of evidence-based medicine, clinical practice is unlikely to be changed without the objective evidence from trials.

In this randomised trial, we hypothesised that recurrence of syncope and presyncope can be reduced by discontinuing/reducing vasoactive therapy without increasing the risk of cardiovascular and neurological events.

METHODS

'Stop vasodepressor drugs in reflex syncope' (STOP-VD) was a randomised, parallel, prospective, trial conducted from January 2014 to March 2016 in four general hospitals, and was registered after approval by the institutional review board. Participants provided written informed consent.

Study participants

All new consecutive referrals to the Syncope Units of the four participating centres were considered to be eligible if: (1) they had experienced ≥2 episodes of suspected or certain reflex syncope during the previous year, while taking at least one vasoactive drug (defined as any antihypertensive agents, nitrates, diuretics, neuroleptic antidepressants or L-dopa antagonists); (2) vasodepressor syncope had been reproduced during tilt-table testing and/or carotid sinus massage; (3) they had no orthostatic hypotension (defined as a symptomatic fall in systolic blood pressure (SBP) ≥20 mm Hg or a decrease to <90 mm Hg); (4) they had no severe hypertension (office BP >150/95) poorly controlled by ongoing therapies, severe structural heart disease or previous transient cerebral ischaemic attack or stroke.

In accordance with the guidelines of the European Society of Cardiology,[2] reflex syncope was considered likely when the clinical features were consistent with a reflex mechanism and competing diagnoses had been excluded. Specifically, we excluded patients with: (a) suspected cardiac arrhythmic syncope (inadequate sinus bradycardia (<50 bpm) or sinoatrial block, second-degree Mobitz I atrioventricular block, second-degree Mobitz II or third-degree atrioventricular block,

paroxysmal tachyarrhythmia or ventricular tachycardia, bundle branch block); (b) severe structural heart disease and/or significant ECG abnormalities, as defined in table 2 of those guidelines;[2] (c) orthostatic hypotension and (d) non-syncopal causes of transient loss of consciousness.

The patients underwent tilt-table testing according to the Italian protocol;[3] the Italian protocol[3] consists of 60–70° passive tilting for 20 min or until syncope occurs. If the passive tilt phase does not induce syncope, 0.3 mg sublingual nitroglycerine is administered while the table is maintained in the same position; the test continues for 15 min after pharmacological challenge. Patients with a dominant vasodepressor form were defined as those who had reproduction of syncope due to hypotension in the absence of asystolic pause >3 s. Patients with a cardioinhibitory response (defined as asystolic pause ≥3 s) were excluded.

The patients underwent carotid sinus massage according to the 'method of symptoms'[2]; patients with a dominant vasodepressor form were defined as those who had reproduction of syncope due to hypotension in the absence of asystolic pause >3 s. Patients with a cardioinhibitory response (defined as asystolic pause ≥3 s) were excluded.

Outcomes

Recurrence of syncope, presyncope or adverse events (defined as stroke, cerebral transient ischaemic attacks, worsening heart failure, myocardial infarction) was used as outcome measures. The primary end point was the combination of syncope, presyncope (if no syncope occurred during the study period) or adverse events.

In accordance with the guidelines of the European Society of Cardiology,[2] syncope was defined as a transient complete loss of consciousness due to transient global cerebral hypoperfusion characterised by rapid onset, short duration and spontaneous complete recovery. Presyncope was defined as the occurrence of the prodromes of syncope, which were not followed by complete loss of consciousness. Other symptoms (eg, dizziness, lightheadedness, weakness, etc), which the patients did not recognise as prodromes of syncope, were excluded from assessment of the end point. Adverse events were verified from patient's clinical records.

Quality of life was assessed 1 month after randomisation by means of the validated self-administered 7-item Specific Symptom Score-Orthostatic Intolerance (SSS-OI) questionnaire.[4] This questionnaire has proved to be able to distinguish patients with progressive (delayed) orthostatic hypotension (total score of 35.2) from healthy matched controls (total score of 10.4).

Randomisation

On completion of baseline assessments, participants were randomly assigned 1:1 to stop/reduce or to continue their vasoactive therapy. Randomisation and assignment to intervention were performed centrally by one of the authors (MB) by means of a computer-generated list, which was blocked per centre. The investigators were blind to the randomisation list.

Interventions

Eligible participants filled in the SSS-OI questionnaire and underwent 24-hour arterial BP monitoring immediately before randomisation. In participants randomised to stop/reduce vasoactive therapy, any vasoactive therapy was discontinued or reduced as much as possible, according to clinical judgement. In participants randomised to continue vasoactive therapy, current therapy was left unchanged. After randomisation, the patients underwent a 1-month run-in period. During this period, they were asked to complete a diary of BP self-measurements performed daily at home at the same hour and to report these values weekly to the investigator. If average BP was 150/90 mm Hg or more, the investigator was recommended to add or increase the dosage of vasoactive therapy, in accordance with recent guidelines on hypertension.[5] After 1 month, patients repeated the SSS-OI questionnaire and supine and standing in-office BP measurement. After this visit, patients were asked to communicate within 1 week the occurrence of any episode of syncope, presyncope or adverse event and were examined every 6 months up to the occurrence of the primary end point or the end of the study.

Statistical methods and power calculation

Continuous data are shown as means±SD or medians (25th–75th percentile), as appropriate, whereas absolute and relative frequencies were used to describe categorical data. The Kolmogorov-Smirnov method was used to check the normality of distributions. Continuous variables were compared by means of Student's t-test or non-parametric Mann-Whitney U test. Fisher's exact test was used for comparison between proportions.

The time to the first occurrence of syncope, presyncope (if no syncope occurred during the study period) or adverse events was analysed by Kaplan-Meier survival curves, which were compared by log-rank test. Analyses were performed using the MedCalc software (Mariakerke, Belgium). Heterogeneity among centres was tested by a stratified Cox model.

The study was powered to address the primary hypothesis that discontinuation/reduction of vasoactive therapy would increase the proportion of event-free survival during follow-up.

An analysis of the literature showed that patients with characteristics similar to those of the present study have approximately 50% syncope recurrence at 2 years, which increases up to 75% if syncope and presyncope are combined together. In the absence of previous evidence, we powered the study around a minimal clinically important difference of a 40% 2-year absolute reduction in the risk of occurrence of the combined primary end point in the stop/reduce group compared with an estimated risk of 75% in the control group. Thus, the study was designed to have 80% power to detect reduction of 40% in the risk of recurrence of the combined primary end point applying a log-rank test with a two-sided significance level of 0.05. This corresponded to a total of 56 patients (28 per group).

Statistical analysis plan

The Lavagna centre coordinated the trial and managed data storage and analysis. Data were entered on paper case-report forms. At the end of the study, each centre filled in an electronic database and delivered it to the coordinating centre. The coordinating centre merged the four databases and performed the statistical analysis. The timing of the first recurrence of syncope, presyncope (if no syncope occurred during the study period) or adverse events, whichever came first, was assessed up to 2 years from randomisation. Patients who withdrew from the study before an outcome were censored at the time of their last observation. Syncope and presyncope were verified within 1 week by recording the nature of the syncopal spell and collateral history from eyewitnesses. A blinded Outcomes Adjudication Committee reviewed patient records and adjudicated outcomes.

RESULTS

Participants

Of 328 initially screened participants, 238 had been taking one or more vasoactive drug for >1 year. In 81 of these, vasodepressor reflex syncope was reproduced during tilt-table testing and/or carotid sinus massage; finally, 58 patients (mean (SD) age, 74 ±11 years) were randomised: 32 were randomised to stop/reduce and 26 to continue vasoactive drug therapy. Of these, 55 participants were included in the analysis (figure 1). Not all patients completed the study: seven withdrew from follow-up prior to any end point (five in the stop/reduce arm and two in the continue arm). Their characteristics are reported in table 1. The mean number of vasoactive drugs per patient was 2.4±1.1 in the 'stop/reduce' group and 2.5±0.9 in the 'continue' group.

Assessment at 1 month

After the run-in period, the mean number of vasoactive drugs per patient was significantly lower in the 'stop/reduce' group than in the 'continue' group: 0.9±1.2 vs 2.4±1.0, p=0.001 (see online supplementary table S1). Consequently, SBP was significantly higher in the 'stop/reduce' group than in the 'continue' group, in both supine (141±13 mm Hg vs 128±14 mm Hg; p=0.004) and standing (133 ±13 mm Hg vs 122±15 mm Hg; p=0.02) positions (table 2). Moreover, SSS-OI questionnaire scores were significantly lower in the 'stop/reduce' group than in the 'continue' group: 7.2±8.8 vs 13.1±10.6, p=0.04 (table 2 and see online supplementary table S2).

Primary outcomes

During a mean follow-up of 13±7 months, the primary combined end point occurred in seven 'stop/reduce' patients (23%): three had syncope, three had presyncope and one had heart failure (who had previously had presyncope). Heart failure developed in a patient aged 88 years affected by hypertensive cardiomiopathy and moderate mitral insufficiency after discontinuation of diuretic, ACE inhibitor and nitrate therapy. Conversely, the primary end point occurred in 13 'continue' patients (54%): 10 had syncope, 2 presyncope and 1 cerebral transient ischaemic attack. The HR was 0.37 (95% CI 0.15 to 0.91) (table 2 and figure 2). No heterogeneity among centres was found: p=0.43. Syncope recurred in 3 'stop/reduce' patients (10%) and in 10 'continue' patients (42%), with a HR of 0.22 (95% CI 0.07 to 0.65) (figure 3). Syncope or presyncope recurred in 7 'stop/reduce' patients (23%) and in 12 'continue' patients (50%), with a log-rank p value of 0.02 and a HR of 0.40 (95% CI 0.16 to 1.00) (figure 4).

The occurrence of clinical end points was independent from baseline SBP values: 120±13 mm Hg in patients with end point versus 128±15 mm Hg in those without (p=0.12).

No patients had trauma secondary to syncope recurrence. No patient died. At the end of follow-up, the mean number of vasoactive drugs per patient remained significantly lower in the 'stop/reduce' group than in the 'continue' group: 1.1±1.5 and 2.3±1.0; p=0.002 (see online supplementary table S1).

DISCUSSION

The main result of this study is that recurrence of syncope and presyncope can be reduced by discontinuing/reducing vasoactive therapy in most elderly patients affected by reflex vasodepressor syncope. Indeed, the strategy of careful BP control, aimed at achieving average SBP values around 140 mm Hg, or at least

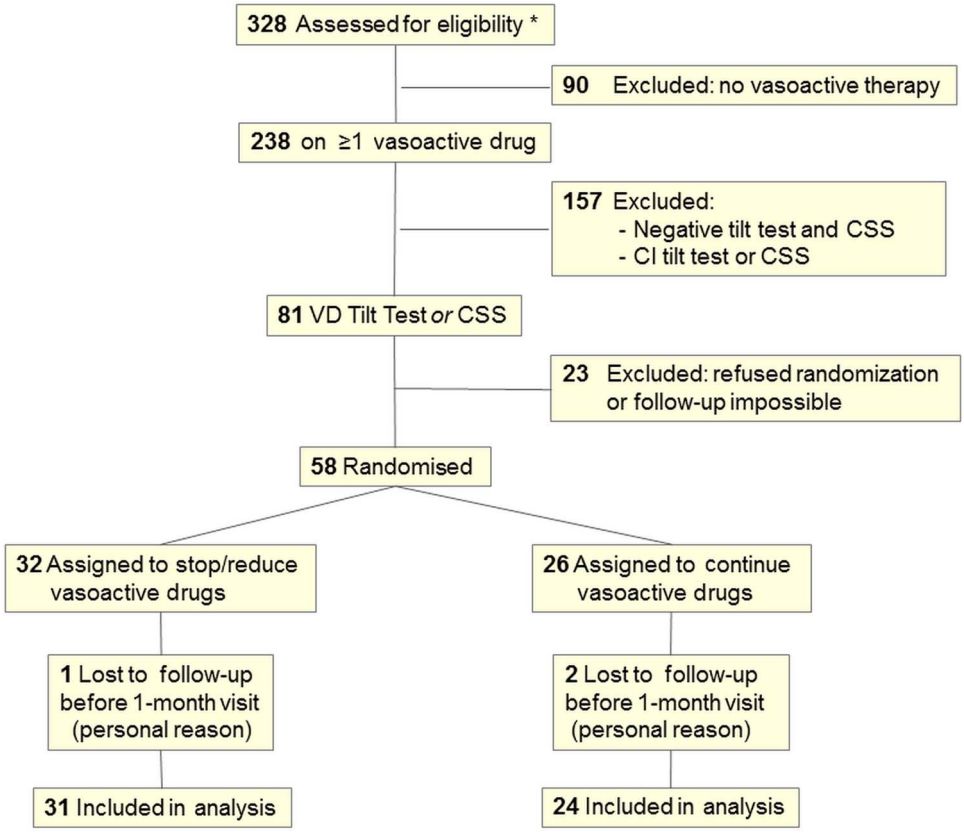

Figure 1 Screening flow. *Criteria for eligibility—suspected or certain reflex syncope, age >40 years—≥2 syncopes/last year. Absence of orthostatic hypotension, no competitive diagnoses, no severe heart failure requiring life-threatening vasoactive therapy, no previous transient cerebral ischaemic attack/stroke. M, mixed; VD, vasodepressor; CSS, carotid sinus syndrome.

Table 1 Characteristics of the patients who completed the study and were analysed for outcome

Clinical characteristics	Stop/reduce therapy (n=31)	Continue therapy (n=24)	p Value
Mean age, years	75±12 (range 46–93)	73±11 (range 46–89)	0.54
Male sex	18 (58%)	10 (42%)	0.28
History of arterial hypertension	29 (94%)	23 (96%)	1.00
History of syncope			
Median lifetime number of syncopes	3.0 (2.0–4.0)	3.0 (2.0–5.0)	0.77
Median number of syncopes in the last year	2.0 (1.3–3.0)	2.0 (1.8–3.0)	0.99
No. of patients with history of syncope >1 year	15 (48%)	14 (58%)	0.59
SSS-OI questionnaire			
Total score (score 0–70), median (IQR)	20 (10–29)	23 (20–32)	0.16
Therapy			
Mean number of vasoactive drugs per patient	2.4±1.1	2.5±0.9	0.77
Class of drug (number of patients)			
ACE inhibitor or Angiotensin Receptor Blocker	27 (87%)	23 (96%)	0.37
α-Antagonist	5 (16%)	5 (21%)	0.73
β-Blocker	7 (23%)	5 (21%)	1.00
Diuretic	12 (39%)	11 (46%)	0.79
Calcium channel blocker	12 (39%)	6 (25%)	0.39
Neuroleptic antidepressant	5 (16%)	5 (21%)	0.73
L-dopa antagonist	2 (6%)	1 (4%)	1.00
Others	2 (6%)	2 (8%)	1.00
Reason for therapy (number of patients)			
Hypertension	29 (94%)	23 (96%)	1.00
Structural heart disease	9 (29)	5 (21%)	0.55
Ischaemic	5 (16%)	3 (12%)	1.00
Non-ischaemic	4 (13%)	2 (9%)	0.69
Atrial tachyarrhythmias	1 (3%)	2 (8%)	0.58
Neurological diseases (Parkinson's disease, encephalopathy)	2 (6%)	3 (12%)	0.64
Depressive disorders	3 (10%)	3 (12%)	1.00
Office arterial blood pressure, mm Hg			
Supine SBP	127±16	122±12	0.19
Standing SBP	119±17	118±14	0.81
Median orthostatic SBP decrease per patient	10 (5–15)	5 (2.3–10)	0.16
24-hour ambulatory blood pressure monitoring, mm Hg			
Mean SBP	120±14	120±11	1.00
Daytime mean SBP	122±12	122±11	1.00
Nighttime mean SBP	115±14	117±13	0.59
Tilt table test			
Positive response	31 (100%)	23 (96%)	0.44
Mixed response	9 (29%)	8 (33%)	0.78
Vasodepressor response	22 (71%)	15 (62%)	0.57
Carotid sinus massage			
Positive vasodepressor response	2 (6%)	2 (8%)	1.00

IRB, SBP, systolic blood pressure; SSS-OI, Specific Symptom Score-Orthostatic Intolerance.

below 150 mm Hg, as per current guideline recommendations,[5] reduced syncopal and presyncopal recurrences without increasing the risk of cardiovascular and neurological events.

In the literature, there are no trials on the discontinuation of vasoactive drug therapy in patients with vasodepressor reflex syncope. Few studies have analysed related topics. Our results are consistent with those of the recently published Systolic Blood Pressure Intervention Trial (SPRINT),[6] which showed that patients at high cardiovascular risk who were already using antihypertensive drugs targeting a SBP of 120 mm Hg had approximately twofold risk of syncope and hypotension than the control group of patients targeting a SBP of 140 mm Hg. van der Velde *et al*[7] tested the effects of the withdrawal of fall risk-increasing drugs in a prospective cohort of 211 geriatric patients. Over a mean follow-up of 6.7 months, there was a significant decrease in orthostatic hypotension and carotid sinus hypersensitivity and a non-significant reduction in positive responses to tilt-table testing; moreover, within a subgroup of fallers, there was a significant decrease in the risk of falls during follow-up in those in whom the above tests had normalised. In a randomised controlled trial of withdrawal of psychotropic medications in 93 patients, Campbell *et al*[8] found a significant reduction in the risk of falling during 44 weeks of follow-up (1.16 vs 0.52 falls per person per year). In an acute randomised trial[9] conducted on 32 patients affected by carotid sinus syncope, withdrawal of vasodilator therapy reduced the magnitude of the vasodepressor reflex induced by carotid sinus massage. This finding was confirmed by a recent observational

Table 2 Primary and secondary outcomes. Results of assessment at 1 month

Outcome	Stop/reduce therapy (n=31)	Continue therapy (n=24)	HR (95% CI)	p Value
Primary combined end point (syncope and/or presyncope and/or adverse event)	7 (23%)	13 (54%)	0.37 (0.15 to 0.91)	0.02
Recurrence of syncope and/or presyncope	7 (23%)*	12 (50%)	0.40 (0.16 to 1.00)	0.035
Recurrence of syncope	3 (10%)	10 (42%)	0.22 (0.07 to 0.65)	0.008
Assessment at 1 month				
Office supine SBP, mm Hg	141±13	128±14		0.001
Office standing SBP, mm Hg	133±13	122±15		0.006
Home daily SBP (average of 30-day measurements)	141±15	133±16		0.06
SSS-OI questionnaire: total score (score 0–70)	7.2±8.8	13.1±10.6		0.04

Adverse events: one patient in the stop/reduce therapy group had an episode of acute heart failure; one patient in the continue therapy group had a cerebral transient ischaemic attack.
*One patient had both an adverse event and presyncope.
SBP, systolic blood pressure; SSS-OI, Specific Symptom Score-Orthostatic Intolerance.

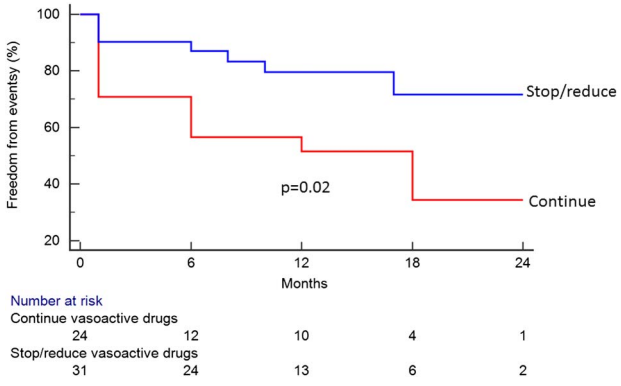

Figure 2 Combined end point of syncope, presyncope and adverse events. The comparison between survival curves was made by log-rank test.

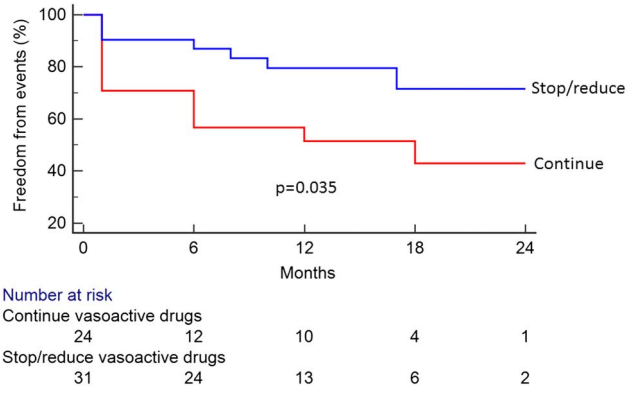

Figure 4 Combined end point of syncope and presyncope. The comparison between survival curves was made by log-rank test.

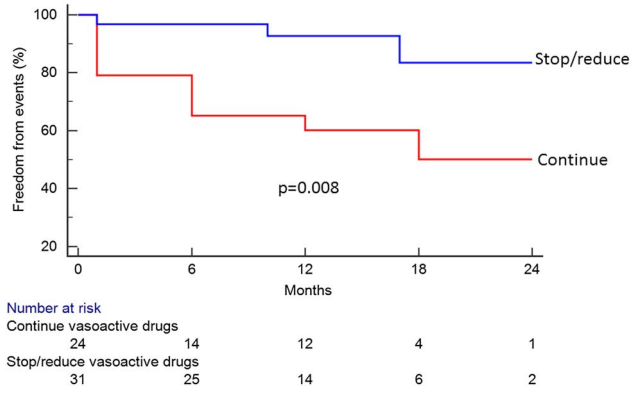

Figure 3 End point of syncope. The comparison between survival curves was made by log-rank test.

study,[10] which demonstrated that reducing/suspending vasoactive therapy in 96 patients affected by carotid sinus syndrome led to a reduction in the burden of syncope from a median of 0.5 syncopes per patient per year to a median 0 syncope per patient per year. Finally, several studies have evaluated the association of vasoactive drugs with orthostatic hypotension and falls; these have yielded contrasting results. To date, no published study has directly linked medication-induced orthostatic hypotension with falls among older patients or evaluated the effects of continuation or withdrawal of therapy in a longitudinal manner.[11 12]

Although adverse events were rare and balanced in both arms of the present study, the safety issue of drug discontinuation needs to be evaluated in a larger population followed-up for a longer time. The recently published SPRINT trial[6] showed that targeting a SBP of 120 mm Hg, as compared with 140 mm Hg, resulted in lower rates of fatal and non-fatal major cardiovascular events (especially heart failure and death from cardiovascular causes), although significantly higher rates of some adverse events were observed in the intensive-treatment group. Thus, translating SPRINT results into our study, the clinical scenario seems to be that of less syncope and better quality of life at the risk of a slight increase in major cardiovascular events. The main objective of the SPRINT trial was mortality and major cardiovascular events. Thus, SPRINT trial was a primary prevention trial of hard clinical end points in which syncope and hypotension were unwanted adverse events, which occurred in <2% of the population.[6] On the contrary, our trial is a secondary prevention trial in which patients were referred specifically for vasodepressor untolerated recurrent syncopes that altered quality of life. Our population cannot be defined as at 'high cardiovascular risk' as was the population of the SPRINT trial. Moreover, there is evidence in the literature[13 14] that reducing SBP to <130 mm Hg by means of antihypertensive therapy in frail elderly patients is associated with worse cognitive

performance and increased mortality. In such a context, the severity of symptoms will finally guide the therapeutic strategy.

Limitations

This study has all the usual limitations of any unblind randomised trial. However, it would have been practically impossible to design a blind trial due to multiple therapies used. Besides, owing to the large variety of therapies at enrolment, it would have been clinically unrealistic and difficult to achieve the adoption of a predefined protocol of stopping/reducing vasoactive drugs. Therefore, the protocol limited to give a general advice to reduce vasoactive therapy as much as possible leaving each investigator the decision how to do based on its clinical judgement.

Both syncope and, especially, presyncope are subjective symptoms. Differentiating presyncope from other symptoms, for example, dizziness, may be difficult. We limited the potential reporting bias by adopting the strict definitions given by the guidelines of the European Society of Cardiology,[2] (see the 'Methods' section). All events were reviewed by a blind adjudication committee. Moreover, results remained significant even when only syncope was considered in analysis.

It is known that the symptoms of reflex syncope overlap with those of orthostatic hypotension. In this study, the average BP on enrolment was within the low/normal range, and some patients were probably being overtreated with vasoactive drugs. However, in those who had recurrence of syncope/presyncope, baseline BP values were not significantly lower than in those without recurrence. Although the SSS-OI questionnaire was developed for patients affected by orthostatic intolerance,[4] it was also able to assess quality of life in patients with reflex syncope, who had a higher total score than healthy controls, but a different spectrum of symptoms from those of orthostatic hypotension. For example, in orthostatic hypotension the most frequently encountered symptoms were dizziness/presyncope, weakness/fatigue and palpitations/hyperhydrosis, accounting for 22/70 points, whereas in the present study these symptoms accounted for only 9.8/70 points, with syncope alone being responsible for 31% of the total score.

Owing to the small sample, we were unable to analyse the differences between different classes of vasoactive drugs in causing syncope. For example, other authors showed that nitrates and diuretics[15] and β-blockers[16] are particularly related to orthostatic hypotension and syncope in older patients. Large trials with a longer follow-up are warranted.

Clinical perspective

The association of vasodepressor reflex syncope with comorbidities requiring chronic vasoactive drug therapy is a frequent clinical problem in the elderly. In this study, 73% of elderly patients with reflex syncope were taking one or more vasoactive drug (figure 1). The present study shows that, in old patients with vasodepressor reflex syncope and low/normal BP values, vasoactive therapy should be discontinued or reduced as the first-choice treatment, in order to achieve the '*not too high, nor too low*' SBP values. Probably, the 'ideal' BP values in patients with vasodepressor syncope is a little bit higher than that resulted from the recent SPRINT trial.[6] An individual careful risk-benefit balance is warranted. The management of patients with high cardiovascular risk or severe hypertension poorly controlled with ongoing therapies remains a challenge and was not addressed in the present study.

Key messages

What is already known on this subject?

Many elderly patients affected by reflex vasodepressor syncope take one or more hypotensive drugs for hypertension, structural heart disease, neurological and psychiatric diseases. Although it is generally believed that vasoactive drugs may have a role in causing vasodepressor reflex syncope, no study has yet evaluated the long-term effects of discontinuation or reduction of such therapies.

What might this study add?

Recurrence of syncope, presyncope could be reduced discontinuing/reducing vasoactive therapy with an HR of 0.22 for syncope and 0.40 for syncope and/or presyncope. Hypertension remained well controlled and few adverse events occurred.

How might this impact on clinical practice?

In old patients with vasodepressor reflex syncope and low/normal blood pressure (BP) values, we modified vasoactive therapy in order to achieve 'not too high, nor too low' systolic BP value of 140 mm Hg.

Contributors MB and DS had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of data analysis. Study concept and design: MB, DS, AU, MT, GG. Acquisition, analysis or interpretation of data: all authors. Drafting of the manuscript: MB, DS. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: MB, DS.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was approved by the institutional review board of each participating centre. Participants provided written informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

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