Annals of Internal Medicine ORIGINAL RESEARCH

Midodrine for the Prevention of Vasovagal Syncope

A Randomized Clinical Trial

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Background: Recurrent vasovagal syncope is common, responds poorly to treatment, and causes physical trauma and poor quality of life. Midodrine prevents hypotension and syncope during tilt tests in patients with vasovagal syncope.

Objective: To determine whether midodrine can prevent vasovagal syncope in usual clinical conditions.

Design: Randomized, double-blind, placebo-controlled clinical trial. (ClinicalTrials.gov: NCT01456481)

Setting: 25 university hospitals in Canada, the United States, Mexico, and the United Kingdom.

Patients: Patients with recurrent vasovagal syncope and no serious comorbid conditions.

Intervention: Patients were randomly assigned 1:1 to placebo or midodrine and followed for 12 months.

Measurements: The primary outcome measure was the proportion of patients with at least 1 syncope episode during follow-up.

Results: The study included 133 patients who had had a median of 6 syncope episodes in the prior year (median age, 32 years; 73% female). Compared with patients receiving placebo, fewer patients receiving midodrine had at least 1 syncope episode (28 of 66 [42%] vs. 41 of 67 [61%]). The relative risk was 0.69 (95% CI, 0.49 to 0.97; $P = 0.035$). The absolute risk reduction was 19 percentage points (CI, 2 to 36 percentage points), and the number needed to treat to prevent 1 patient from having syncope was 5.3 (CI, 2.8 to 47.6). The time to first syncope was longer with midodrine (hazard ratio, 0.59 [CI, 0.37 to 0.96]; $P = 0.035$; log-rank $P = 0.031$). Adverse effects were similar in both groups.

Limitation: Small study size, young and healthy patients, relatively short observation period, and high proportion of patients from 1 center.

Conclusion: Midodrine can reduce the recurrence of syncope in healthy, younger patients with a high syncope burden.

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For author, article, and disclosure information, see end of text.
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* For members of the POST 4 (Prevention of Syncope Trial 4) investigators, see the **Appendix** (available at Annals.org).

Vasovagal syncope is common and causes physical trauma (1, 2) and poor quality of life (3, 4). It can be difficult to treat because no current medications have high-quality evidence for effectiveness (5–7). Midodrine holds promise for preventing the recurrence of vasovagal syncope. It is a prodrug that is converted to desglymidodrine, which is an α_1-adrenergic receptor agonist and a direct vasoconstrictor and venoconstrictor. It may prevent reduced cardiac output due to decreased preload, which is an early feature of the vasovagal reflex (8–10).

Three randomized studies reported the ability of midodrine to prevent syncope on tilt tests (11–13). Two subsequent randomized trials tested whether midodrine prevents clinical vasovagal syncope (12, 14). One was small and short-term and studied children (12), whereas the other was open-label and not placebo-controlled (14). The lack of high-quality evidence for the clinical effectiveness of midodrine has led to weak recommendations in guidelines for syncope management (5–7).

Given the limited evidence for the effectiveness of other medical treatment options and weak recommendations for the use of midodrine, we did a clinical trial to assess whether midodrine could prevent the recurrence of vasovagal syncope.

Methods

Patient Eligibility

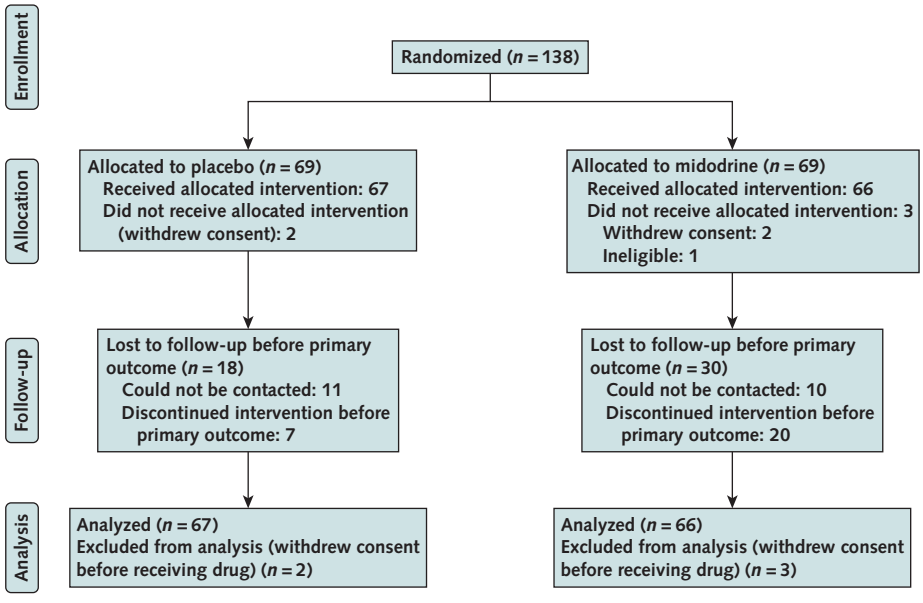
The study was approved by ethics review committees in all study centers. Patients were eligible if they were aged 18 years or older, had a Calgary Syncope Symptom Score of at least 2 (15), and had fainted at least twice in the year before enrollment (16). Patients were excluded if they had any of the following conditions: other causes of syncope; inability to give informed consent; important valvular, coronary, myocardial, or conduction abnormality or arrhythmia; hypertrophic cardiomyopathy; permanent pacemaker; seizure disorder; urinary retention; hypertension above 140/90 mm Hg; liver disease; glaucoma; postural orthostatic tachycardia syndrome (17) or orthostatic hypotension; or prior use of midodrine.

See also:

Editorial comment 1460
Summary for Patients I-28

Web-Only
Supplement

Figure 1. Study flow diagram.



The reasons for withdrawal of the study drug in the placebo group were adverse effects ($n = 2$), stopped fainting ($n = 1$), continued fainting ($n = 2$), study fatigue ($n = 1$), and lost contact ($n = 1$). The reasons for withdrawal of the study drug in the midodrine group were adverse effects ($n = 2$), stopped fainting ($n = 1$), continued fainting ($n = 5$), study fatigue ($n = 1$), family doctor preference ($n = 1$), other ($n = 3$), and lost contact ($n = 6$).

Patient Education

All patients were taught the pathophysiology of vasovagal syncope; reassured about its benign nature; and provided advice on conservative measures (5–7) to prevent vasovagal syncope, including physical maneuvers (18) and dietary advice that emphasized fluid and sodium intake (19).

Randomization and Study Treatment

Investigators or coordinators at each center randomly assigned patients in a double-blind fashion using permuted blocks of 2, 4, and 6 to receive midodrine or a matching placebo for 1 year. Randomization was done centrally with a separate scheme developed for each center using a computerized algorithm. Medication containers were filled and labeled with the randomization code number centrally. The study coordinators started dosing with 5 mg of study drug or placebo 3 times daily, 4 hours apart, during daylight hours, with the intent to adjust the dose of drug or placebo as tolerated within a range of 2.5 mg twice daily, 4 hours apart, up to 10 mg, 3 times daily, every 4 hours. We strongly suggested that dose ranging be completed within the first 2 weeks. If intolerable symptoms persisted despite dose reductions, the drug or placebo was withdrawn and the patient released from the study. Unless unavoidable, patients were not permitted to receive the following treatments until after the primary outcome event: permanent pacemakers, β-blockers, other α_1-adrenergic agonists or antagonists, tricyclic antidepressants, serotonin reuptake inhibitors, scopolamine, theophylline, or fludrocortisone. Use of nonstudy medications was recorded. All study personnel remained blinded throughout the study.

Power Calculations

The study was powered to address the primary hypothesis that patients receiving midodrine would have a lower recurrence of syncope than those receiving placebo in an intention-to-treat analysis. Published data (11–14) suggested a relative risk reduction of 68%, but we powered this study using a more conservative relative risk reduction of 55%. Over a 1-year observation period, this assumption would equate to a reduction from 55% to 25% of patients having a syncope recurrence. Using an α level of 0.05, we calculated that a study sample of 128 patients with a 1-year follow-up provided 80% power and allowed for an anticipated 20% loss to follow-up.

Outcomes

The outcome was syncope, and 3 measures of the outcome were possible: time to first recurrence of syncope, frequency of syncope, and proportion of patients with syncope. On the basis of our experience with patients who have this condition, we believed that patients care most whether they faint at all. Therefore, we used the proportion of patients with a syncope recurrence as the primary outcome measure (20, 21), and we classified treatment as having failed if a patient had at least 1 syncope episode within the 12-month observation period. We posted this measure as the primary outcome in ClinicalTrials.gov (NCT01456481) on 20 October 2011, and data analysis began on 18 December 2018. Syncope was verified within 1 week by recording its characteristics; collateral history; and physical examination for signs of injury, such as abrasions, contusions, and fractures. Outcomes were adjudicated by a blinded outcomes adjudication committee. Secondary analyses included the frequency of syncope and

time to first syncope recurrence, where we used time-to-event analysis, censoring patients if they were lost to follow-up (LTFU) for any reason before a first syncope.

Other prespecified secondary outcomes included presyncope measured by the Calgary Presyncope Scale, quality of life measured by the EuroQol 5-dimension instrument, and the effect of syncope on quality of life measured by the Impact of Syncope on Quality of Life questionnaire. These results will be reported separately. We also planned to measure biomedical outcomes, but these studies remain unfunded.

Statistical Analysis

The primary intention-to-treat analysis included all patients who ingested at least 1 tablet of the randomized allocated intervention, and we analyzed patients according to their randomized allocation if they subsequently withdrew from treatment (22). We also did a prespecified landmark analysis (23) that included all patients who remained in the study after 2 weeks, but we did not count events that occurred during the first 2 weeks, when some patients may not yet have reached the target dose for midodrine. We did not do the interim analysis that was specified in our protocol (**Supplement**, available at Annals.org). All levels of significance are 2-sided. Continuous data are presented as medians and interquartile ranges (IQRs; 25th to 75th percentile). Differences in age, sex, and number of syncope episodes in the prior year between those LTFU and those staying in the study were reported using medians and IQRs. The Fisher exact test was used to compare the proportions of patients with a syncope recurrence. We used the Wald approach to calculate the CIs for the relative risks.

The times to first syncope were depicted using the Kaplan-Meier estimate. Differences between treatments in the incidence curves were tested using log-rank statistics, and we used hazard ratios (HRs) from Cox proportional hazards models to compare time to first syncope between the 2 groups. Covariates were not included in these models. We repeated our analyses of proportions with syncope and time to syncope in the landmark cohort of patients who remained in the study after 2 weeks. We assessed the consistency of treatment effects within subgroups defined using prespecified numerical variables (age, heart rate, prior-year syncope episodes, and systolic blood pressure [BP]) and categorical variables (sex; Calgary vs. other study centers). Subgroups for numerical variables were determined using median values from the intention-to-treat cohort. Subgroup-by-treatment interactions for the primary outcome were tested using logistic regression models.

To assess proportional hazards assumptions for the Cox models, we tested whether an association existed between time and the scaled Schoenfeld residuals (24). The risk for failure for patients LTFU in the treatment group might have increased once the patients stopped receiving medication. As a sensitivity analysis, we calculated the HR in a gamma-imputation model that imputed failures for patients LTFU in the midodrine group, assuming that risk for treatment failure was equal between groups in patients LTFU (25).

Statistical analysis was done using R, version 4.0.2 (R Foundation). The table2x2 function from the Publish package 2019.12.04 was used for Fisher exact tests, and the survfit and coxph functions from the survival package 3.1-12 were used to calculate the Kaplan–Meier cumulative incidence curves and fit the Cox proportional hazards models, respectively. The glm function from the stats package 4.0.2 was used for the logistic regression analyses to test subgroup interactions. The gammaImpute and ImputeStat functions of the InformativeCensoring package 0.3.5 were used for the gamma-imputation model.

Role of the Funding Source

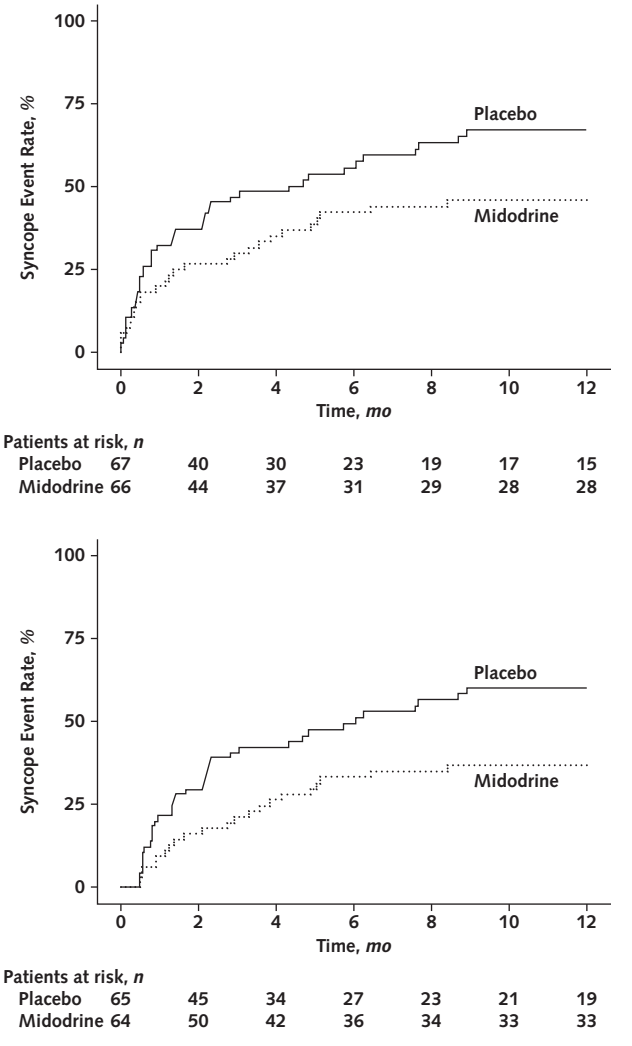
This study was funded by the Canadian Institutes of Health Research, placebo was provided gratis by Shire Pharmaceuticals and Apotex, and the companies provided active drug at cost. None of these funders had any role in the design, conduct, or analysis of the study or in the decision to submit the manuscript for publication. The authors

Table 1. Baseline Characteristics of Study Treatment Groups

Characteristic	Placebo (*n* = 67)	Midodrine (*n* = 66)
Median age (IQR), *y*	35 (27–47)	31 (25–43)
Female sex, *n (%)*	50 (75)	48 (72)
Syncope history		
Median age of onset (IQR), *y*	18 (14–27)	17 (14–25)
Median lifetime syncope episodes (IQR), *n*	23 (11–250)	21 (10–100)
Median symptom duration (IQR), *y*	14 (4–25)	14 (3–26)
Median syncope frequency (IQR), *episodes/y*	5 (1–20)	4 (1–9)
Median Calgary Syncope Symptom Score (IQR)	3 (1–5)	3 (1–4)
Median syncope episodes in previous year (IQR), *n*	7 (4–25)	5 (3–12)
Previous medical therapy for syncope, *n*		
Salt supplements	21	25
Increased fluid	33	34
Fludrocortisone	8	11
β-Blocker	12	9
Disopyramide	1	1
SSRI	5	5
Median supine systolic BP (IQR), *mm Hg*	118 (110–127)	116 (108–124)
Median supine heart rate (IQR), *beats/min*	68 (62–81)	72 (62–82)

BP = blood pressure; IQR = interquartile range; SSRI = selective serotonin reuptake inhibitor.

Figure 2. Syncope recurrence rates.



Top. Cumulative incidence of first syncope in each treatment group in the primary intention-to-treat analysis. **Bottom**. Probability of incidence of first syncope in the landmark sample after the 2-wk dose stabilization period in each assigned treatment group.

had full access to the data and take responsibility for its integrity. The University of Calgary Syncope Clinic coordinated the trial and managed data storage and analysis.

RESULTS

Sample Characteristics

From February 2012 to October 2017, a total of 138 consenting patients were randomly assigned in 25 university hospitals in Canada, the United States, Mexico, and the United Kingdom. The trial stopped 1 year after the last patient was enrolled. Of these 138 patients, 5 withdrew before taking the first pill and were excluded from the final analysis (**Figure 1**). Of the remaining 133 participants (73% female), 66 were in the midodrine group and 67 in the placebo group. Patients had a median age of 32 years and started having syncope at a median age of 17 years. Before randomization, patients had had a median of 21 syncope episodes (IQR, 10 to 150 episodes) over a median of 14 years (IQR, 4 to 25 years), with a median frequency of 4.1 episodes (IQR, 1.1 to 13.7 episodes) per year. They had had a median of 6 syncope episodes (IQR, 3 to 20 episodes) in the year before randomization. The median Calgary Syncope Symptom Score of included patients was 3 (IQR, 1 to 4), and 18 patients had been injured because of syncope. Few patients had comorbid conditions. At baseline, the median supine heart rate was 70 beats/min and the median supine BP was 117/73 mm Hg. The 2 study samples were well balanced in their baseline demographic and clinical variables (**Table 1**).

In all, 56 of 66 patients in the midodrine group and 56 of 67 in the placebo group were followed at least until their first syncope episode or for the full 12 months (**Figure 1**). The median follow-up times for the 10 midodrine and 11 placebo patients LTFU before an outcome were 2.43 months and 2.53 months, respectively. A further 27 stopped taking their assigned medication but continued to be followed (20 in the midodrine group and 7 in the placebo group).

In the midodrine group, the median age was 23 years (IQR, 21 to 27 years) for those LTFU before an outcome and 31 years (IQR, 27 to 44 years) for those completing the study. In the placebo group, these median ages were 32 years (IQR, 24 to 35 years) and 36 years (IQR, 27 to 46 years), respectively. In the midodrine group, the number of syncope episodes in the previous year was 4 (IQR, 2.0 to 7.3) for those LTFU before an outcome and 5.0 (IQR, 3.0 to 13.3) for those completing the study. In the placebo group, these values were 5.0 (IQR, 2.0 to 25) and 7.5 (IQR, 4.0 to 24), respectively.

Study Medication

The median of the last dose was 7.5 mg (IQR, 5.0 to 10.0 mg) in the midodrine group and 10 mg (IQR, 5.0 to 10.0 mg) in the placebo group. In the midodrine group, the median dose was 5.0 mg (IQR, 5.0 to 10.0 mg) for those with a syncope episode (n = 28), 6.25 mg (IQR, 5.0 to 10.0 mg) for those LTFU (n = 10), and 8.75 mg (IQR, 2.5 to 10.0 mg) for those who did not have syncope in 12 months (n = 28). In the placebo group, the median dose was 7.5 mg (IQR, 5.0 to 10.0 mg) for those with a syncope episode (n = 41), 5.0 mg (IQR, 2.5 to 10.0 mg) for those LTFU (n = 11), and 10.0 mg (IQR, 5.0 to 10.0 mg) for those who did not have syncope in 12 months (n = 15). Only 19 participants in the midodrine group and 16 in the placebo group were taking medications discouraged by the study protocol (**Supplement**).

Adverse effects occurred in 29 participants in the midodrine group and 25 in the placebo group. Paresthesia and piloerection were reported by 12 patients in the midodrine group and 8 in the placebo group. Headache (6 and 5 patients, respectively), nausea (4 and 3 patients, respectively), and other adverse events were balanced between the 2 groups. Two patients withdrew from midodrine because of hypertension, and 2 withdrew from placebo because of headache and nausea.

Primary Outcomes

In the intention-to-treat analysis, midodrine was associated with a lower likelihood of having a recurrence of syncope (28 of 66 patients [42%] vs. 41 of 67 patients [61%]; absolute risk reduction, 19 percentage points [95% CI, 2 to 36 percentage points]). The number needed to treat to prevent 1 patient from having syncope was 5.3 (CI, 2.8 to 47.6). The relative risk for syncope recurrence with midodrine was 0.69 (CI, 0.49 to 0.97; $P = 0.035$). The actuarial syncope event rates over 1 year (**Figure 2**, *top*) were 46.0% in the midodrine group and 67.3% in the placebo group (log-rank $P = 0.031$). Midodrine was associated with a longer time to first recurrence of syncope (HR, 0.59 [CI, 0.37 to 0.96]; $P = 0.035$).

The midodrine group had 73 syncope episodes, and the placebo group had 146. Among patients with at least 1 syncope recurrence (**Figure 3**), median syncope frequencies were 0.32 (IQR, 0.12 to 0.75) and 0.30 (IQR, 0.11 to 1.00) syncope episodes per month in the midodrine and placebo groups, respectively. Few patients were injured from a syncope (midodrine, 7 of 28 patients [25%] with 9 events; placebo, 11 of 41 patients [27%] with 30 events).

Landmark Analysis

The protocol (**Supplement**) assigned an initial 2-week period for study personnel and patients to achieve a final daily dose of study medication. Four patients who received study medication withdrew within the first 2 weeks. Of the remaining patients, 22 of 64 (34%) who received midodrine had at least 1 syncope episode after week 2, compared with 37 of 65 (57%) who received placebo. In all patients who remained in the study after 2 weeks, the absolute risk reduction due to midodrine was 23 percentage points (CI, 6 to 39 percentage points), with a number needed to treat to prevent 1 patient from having syncope over 1 year of 4.4 (CI, 2.5 to 17.2). The relative risk for syncope recurrence with midodrine was 0.60 (CI, 0.41 to 0.90; $P = 0.013$). The actuarial syncope event rates over 12 months (**Figure 2**, *bottom*) in the 129 patients in the midodrine and placebo groups were 37% and 61%, respectively (log-rank $P = 0.011$). The HR for time to first syncope was 0.51 (CI, 0.30 to 0.86; $P = 0.012$).

Tests of Assumptions

No evidence suggested that the proportional hazards assumption was violated in any of the Cox models. In the gamma-imputation model, which imputed syncope times for patients LTFU on the basis of the risk for syncope for the placebo group, there was a modest attenuation of effect (HR, 0.62 [CI, 0.38 to 0.99]).

Subgroup Analyses

We found no significant interaction of treatment with relative risk for syncope by patient age, sex, number of syncope episodes in the previous year, or baseline heart rate. The treatment effect may interact with the relative risk for syncope on the basis of baseline systolic BP ($P = 0.030$). The relative risk for midodrine versus placebo was 0.53 (CI, 0.32 to 0.88) in patients with a systolic BP higher than 120 mm Hg and 0.92 (CI, 0.55 to 1.52) in those with a systolic BP of 120 mm Hg or lower (**Table 2**). No evidence indicated that the effect of midodrine in Calgary, where 45% of participants were enrolled, differed from that in other sites ($P = 0.63$).

Discussion

This multicenter, international, randomized, double-blind, placebo-controlled trial showed that midodrine is effective in reducing the likelihood of a syncope recurrence in younger patients with frequent syncope when it is administered in conjunction with guideline-directed teaching about lifestyle risk reduction (5–7).

There is a pressing need for effective treatments for vasovagal syncope. Increased salt and fluid intake (19, 26) is commonly advised, but this strategy has not been validated by clinical trials. Counterpressure maneuvers prevented syncope in open-label randomized studies (18) but have not been tested against placebo maneuvers. Fludrocortisone prevented syncope in a randomized, placebo-controlled study (21), but only in a secondary landmark analysis (23). The effectiveness of selective serotonin reuptake inhibitors is uncertain (27, 28). Patients with syncope and asystole during positive tilt tests may benefit from dual-chamber pacing with closed loop stimulation (29, 30), but those with asystole during syncope and positive tilt tests do not benefit from other dual-chamber pacing (31, 32). β-Blockers might be effective in older patients (20, 33).

This study provides direct evidence for the effectiveness of midodrine in preventing recurrent vasovagal syncope in younger patients with frequent syncope. There is a physiologic rationale for the effectiveness of midodrine. Vasovagal syncope is often preceded by orthostatic stress, and upright positions cause dependent pooling of up to 800 mL of venous blood. Patients with vasovagal syncope at times have ineffective venoconstriction (34–36), causing dependent venous pooling. This process in turn decreases cardiac output, resulting in hypotension and eventually decreased cerebral perfusion and unconsciousness (36). Despite an initial sympathetic surge in response to decreased cardiac output, a paradoxical vasodilation may occur in these patients (9, 10), leading to further hypotension and transient loss of consciousness.

Figure 3. Syncope episodes per month in follow-up in patients randomly assigned to midodrine or placebo.

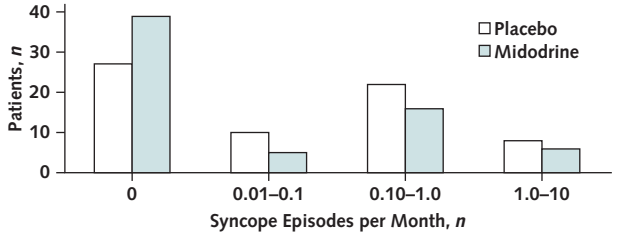


Table 2. Estimated Treatment Effects in Subgroup Analyses*

Variable	Syncope Episodes, *n/N (%)*		Midodrine Relative Risk (95% CI)	*P* Value*
	Placebo	Midodrine		
Age				
≤30 y	19/28 (68)	13/30 (43)	0.64 (0.39–1.03)	0.62
>30 y	22/39 (56)	15/36 (40)	0.74 (0.43–1.16)	
Sex				
Female	33/50 (66)	20/47 (43)	0.64 (0.44–0.95)	0.34
Male	8/17 (47)	8/19 (42)	0.89 (0.43–1.86)	
Prior year syncope episodes				
≤3 episodes	4/15 (27)	5/25 (20)	0.75 (0.24–2.36)	0.75
>3 episodes	37/52 (71)	23/41 (56)	0.79 (0.57–1.09)	
Systolic BP				
≤120 mm Hg	17/39 (44)	18/45 (40)	0.92 (0.55–1.52)	0.026
>120 mm Hg	24/28 (88)	9/20 (45)	0.53 (0.32–0.88)	
Heart rate				
≤70 beats/min	17/35 (49)	12/28 (43)	0.88 (0.51–1.52)	0.118
>70 beats/min	24/32 (75)	16/38 (42)	0.56 (0.37–0.86)	
Study center				
Calgary	15/30 (50)	12/30 (40)	0.74 (0.49–1.14)	0.34
Not Calgary	26/37 (70)	16/36 (44)	0.61 (0.34–1.07)	

BP = blood pressure.
* Probability value from test of subgroup-by-treatment interaction from logistic regression model.

Midodrine's active metabolite increases cardiac output and peripheral resistance (37). No previously published studies provided high-quality evidence for its clinical effectiveness (38), although 3 proof-of-principle tilt-test studies had positive findings (11–13). In addition, midodrine reduced syncope recurrences in a 6-month follow-up study of 26 children (12) and in an open-label randomized clinical trial of 61 participants followed for up to 1 year (14). We designed this study to address the remaining gaps in our knowledge.

After a landmark dose adjustment period of 2 weeks, this study detected a 40% relative risk reduction of recurrent syncope, which is statistically and clinically significant (relative risk, 0.60 [CI, 0.41 to 0.90]). The absolute risk reduction was about 19 percentage points (CI, 2 to 36 percentage points), with a number needed to treat to prevent syncope of 5 (CI, 2.8 to 47.6). Therefore, 4 of 5 patients received midodrine without clinical benefit. The study sample patients were highly symptomatic, having had a median of 23 lifetime syncope episodes and 5 syncope episodes in the preceding year. In these circumstances, taking a medication 3 times a day seems worth the effort. In contrast, it may not be worth the effort for patients with less frequent events. In addition, the high prevalence of hypertension in older patients will limit midodrine's use in that population. In subgroup analyses, no patient subgroups, other than those with higher baseline BP, seemed to benefit more or less than the average study patient. The drug is reasonably well tolerated, with adverse effects that included supine hypertension, nausea, scalp paresthesias, piloerection, and rash. Additional contraindications to the use of midodrine include hypertension, heart failure, urinary retention, glaucoma, and liver disease, and patients with these disorders were excluded from this study. Therefore, the patients most likely to benefit are younger patients with a high syncope burden who do not have hypertension or contraindications to midodrine use.

The similar syncope frequencies in patients who continued to faint while receiving midodrine versus placebo suggests that there may be responders and nonresponders. The alternative model—that all patients are improved somewhat—would have caused a leftward shift in the distribution of patients receiving midodrine. It is worth remembering that vasovagal syncope often occurs in clusters, and periodic drug withdrawal would be a worthwhile strategy.

The study was limited by its small size, an observation period that was brief relative to the condition's long duration, the restriction of the study to young and otherwise healthy participants, and the high proportion of patients from 1 center. In addition, in the primary analysis some patients had syncope before the target midodrine dose was achieved. However, both the primary and landmark analyses showed a benefit that was statistically and clinically significant. Twenty-one patients dropped out of the study before an event or the completion of the trial, but only 2 patients in each group withdrew because of perceived adverse effects. The remainder dropped out because they did not want to continue and because of other preferences unrelated to adverse effects, and the total number of dropouts in each group was about equal (10 in the midodrine group and 11 in the placebo group). Therefore, dropouts probably did not substantially affect the study's results. A further 27 participants stopped taking their assigned medication but continued to be followed in

the study, but these participants likely would bias the results against midodrine. Because the follow-up was limited to 1 year, we could not assess the long-term adherence and effectiveness of midodrine. Finally, the gamma-imputation model found only a modest attenuation of the treatment effect by informative censoring (HR, 0.62 [CI, 0.38 to 0.99]).

In conclusion, in this study of younger, healthy patients with frequent recurrences of vasovagal syncope, oral midodrine significantly decreased the proportion of patients with recurrent syncope when it was administered in conjunction with guideline-directed teaching about lifestyle risk reduction.

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Data Sharing Statement: The authors have indicated that they are willing to share the data but that it will require an agreement about the specific fields, purposes, and attributions (contact Robert Sheldon; e-mail, sheldon@ucalgary.ca).

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Appendix: POST 4 (Prevention of Syncope Trial 4) Investigators

The following centers and investigators participated in POST 4, with the number of participants listed in parentheses: The University of Calgary, Calgary, Alberta, Canada (60): R. Sheldon*, D. Ritchie*, M. McCrae†, C. Eronmwon†, and S. Safdar*; University of Sherbrooke, Sherbrooke, Quebec, Canada (10): F. Ayala-Paredes* and C. Jean†; Hamilton Health Sciences Centre, Hamilton, Ontario, Canada (8): C.A. Morillo*, J. Guzman*, R. Chinchilla†, and A. Frechette†; Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico (8): M. Marquez*, T. Ruíz-Siller†, G. Luna-Limón†, P. del Rivero-Morfin†, A. Reyes-Quintero†, and L. Fernández-González†; Victoria Heart Institute, Victoria, British Columbia, Canada (4): A. Tang*, R. Leather†, D. Parfett†, and C. Patterson†; Sacre Coeur Hospital, Montreal, Quebec, Canada (4): T. Kus* and A. Langlois†; Vanderbilt University Medical Center, Nashville, Tennessee (4): S.R. Raj* and B. Black†; University of Minnesota, Minneapolis, Minnesota (4): D. Benditt† and J. Dicken†; Institute de Cardiologie de Montreal, Montreal, Quebec, Canada (4): M. Talajic† and M.J. Billo†; Queen Elizabeth II Hospital, Halifax, Nova Scotia, Canada (3): R. Parkash†, A. Fearon†, and K. Giddens†; South Tees Hospitals, South Tees, United Kingdom (2): N. Linker† and B. Atkinson†; Musgrove Park Hospital, Taunton, United Kingdom (2): M. Dayer† and H. Mills†; Imperial College Healthcare, United Kingdom (2): B. Lim† and R. Elliot†; Wellmont CVA Heart Institute, Kingsport, Tennessee (2): A. Rao† and T. Stover†; Université Laval, Quebec City, Quebec, Canada (2): I. Nault†, J. Robinson†, and B. Ottinger†; Horizon Health, Saint John, New Brunswick, Canada (2): R. Bessoudo† and G. O'Blenis†; Ottawa Heart Institute, Ottawa, Ontario, Canada (2): A. Tang*, D. Birnie†, and K. MacDonald†; London Health Sciences Centre, London, Ontario, Canada (2): A. Tang*, L. Nyman†, and M. Shillington†; St. Boniface General Hospital, Winnipeg, Manitoba, Canada (1): C. Seifer† and R. Fromm†; Regina General Hospital, Regina, Saskatchewan, Canada (1): O. Sultan† and S. Kelly†; Royal Alexandra Hospital, Edmonton, Alberta, Canada (1): R. Williams† and S. Martin†; King's College Hospital, London, United Kingdom (1): N. Gall†, K. Martin†, and R. Williams†; University of Alberta Hospital, Edmonton, Alberta, Canada (1): R. Sandhu†; New York Medical College, New York, New York (1): J. Stewart† and C. Terilli†; Newcastle upon Tyne Hospitals, Newcastle, United Kingdom (1): S. Parry† and P. McAlinden†; and University Hospitals Coventry & Warwickshire, Coventry, United Kingdom (1): S. Hayat†, A. Padwick†, and V. Ansell†.

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