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ORIGINAL INVESTIGATIONS

Fludrocortisone for the Prevention of Vasovagal Syncope

A Randomized, Placebo-Controlled Trial

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ABSTRACT

BACKGROUND There is limited evidence whether being on fludrocortisone prevents vasovagal syncope.

OBJECTIVES The authors sought to determine whether treatment with fludrocortisone reduces the proportion of patients with recurrent vasovagal syncope by at least 40%, representing a pre-specified minimal clinically important relative risk reduction.

METHODS The multicenter POST 2 (Prevention of Syncope Trial 2) was a randomized, placebo-controlled, double-blind trial that assessed the effects of fludrocortisone in vasovagal syncope over a 1-year treatment period. All patients had >2 syncopal spells and a Calgary Syncope Symptom Score >−3. Patients received either fludrocortisone or matching placebo at highest tolerated doses from 0.05 mg to 0.2 mg daily. The main outcome measure was the first recurrence of syncope.

RESULTS The authors randomized 210 patients (71% female, median age 30 years) with a median 15 syncopal spells over a median of 9 years equally to fludrocortisone or placebo. Of these, 96 patients had ≥1 syncope recurrences, and only 14 patients were lost to follow-up before syncope recurrence. There was a marginally nonsignificant reduction in syncope in the fludrocortisone group (hazard ratio [HR]: 0.69: 95% confidence interval [CI]: 0.46 to 1.03; $p = 0.069$). In a multivariable model, fludrocortisone significantly reduced the likelihood of syncope (HR: 0.63; 95% CI: 0.42 to 0.94; $p = 0.024$). When the analysis was restricted to outcomes after 2 weeks of dose stabilization, there was a significant benefit due to fludrocortisone (HR: 0.51; 95% CI: 0.28 to 0.89; $p = 0.019$).

CONCLUSIONS The study did not meet its primary objective of demonstrating that fludrocortisone reduced the likelihood of vasovagal syncope by the specified risk reduction of 40%. The study demonstrated a significant effect after dose stabilization, and there were significant findings in post hoc multivariable and on-treatment analyses. (A randomised clinical trial of fludrocortisone for the prevention of vasovagal syncope; ISRCTN51802652; Prevention of Syncope Trial 2 [POST 2]; NCT00118482) (J Am Coll Cardiol 2016;68:1-9) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HR = hazard ratio

IQR = interquartile range

Vasovagal syncope is a common problem that reduces quality of life (1) and can be difficult to treat (2). No therapies have been proven effective by randomized controlled trials (2), with the exception of pacemakers for older patients with documented asystole during syncope (3). Although fludrocortisone is recommended to prevent syncope (4), no clinical studies have tested its effectiveness in adults.

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The rationale for fludrocortisone is based on the importance of venous return in the physiological cascade leading to the vasovagal reflex (5–7), although there is no direct evidence that fludrocortisone serves this function. Most syncope occurs during upright positions, and head-up tilt alone can induce syncope (2,8). The vasovagal reflex is preceded by reduced cardiac output due to decreased pre-load (5–7) and, when induced by tilt testing, it can be prevented by saline infusion (9,10). Two observational studies reported that fludrocortisone improved clinical outcome in children (9,10), but a small, pediatric randomized trial reported that fludrocortisone worsened outcome (11).

Given the lack of evidence for the effectiveness of other medical treatment options, the recommended use of fludrocortisone, and the lack of evidence for its effectiveness, it seemed important to more formally test the effectiveness of this agent. Therefore, we performed a multicenter, double-blind, placebo-controlled, dose-ranging randomized clinical trial of fludrocortisone to assess its benefit in preventing vasovagal syncope.

METHODS

Ethics review committees in all centers approved the study. Study methodology has been published (12). Patients were eligible if they were ≥14 years of age, had a score >−3 on the Calgary Syncope Symptom Score (13), and had >2 lifetime syncopal spells (14), which predicts a risk of syncope in the next year of >40%. Patients were excluded if they had other causes of syncope; could not provide informed consent; had significant comorbidities, a permanent pacemaker, glaucoma, diabetes mellitus, hepatic disease, blood pressure (BP) ≥130/85 mm Hg, or had a clinical need for or contraindication to fludrocortisone; or had previously used fludrocortisone for the treatment of vasovagal syncope. Patients were excluded if, during a 5-min stand test, they had postural tachycardia (15) (heart rate increase ≥30 beats/min) or orthostatic hypotension (BP decrease ≥20/10 mm Hg). Patients were randomized in syncope and arrhythmia clinics, and each center completed a screening log of eligible, nonrandomized patients. All patients were taught the causes of vasovagal syncope; reassured about its outcome; advised to increase sodium, potassium, and fluid intake; and taught physical counterpressure maneuvers (16,17).

RANDOMIZATION AND STUDY TREATMENT. Randomization by computer was stratified by center into blocks of 4 in 2 parallel arms. One of the authors (M.S.R.) generated the allocation sequence, and the patients were assigned to their groups by investigators and coordinators. The subjects were allocated 1:1 to receive fludrocortisone or a matching placebo from coded, numbered containers for a period of 1 year. All investigators and subjects were blinded throughout the study. Treatment started with 0.1 mg of study drug daily with the intent to increase to 0.2 mg daily within 5 to 14 days. Patients who were intolerant of the study medication had the dose reduced to 0.05 mg daily. If intolerable symptoms persisted or the patient withdrew consent, the medication was discontinued, but patient follow-up continued when possible. We requested that patients not receive permanent pacemakers, beta-blockers, alpha-adrenergic agonists or antagonists, antidepressants, scopolamine, theophylline, or nonstudy fludrocortisone, although they

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were not a cause for release from the study. Use of nonstudy medications was recorded.

STATISTICAL ANALYSIS. The study was powered to address the primary hypothesis that a decision to treat patients with fludrocortisone up to 0.2 mg daily would increase the proportion of patients without a syncope recurrence compared with placebo. In the absence of evidence regarding fludrocortisone effectiveness, we powered the study for a minimal clinically important 40% relative risk reduction, defined after extensive international consultations with syncope experts. We estimated the entry criteria would provide a risk of syncope in the control and fludrocortisone arms of 40% and 24%, respectively, with a combined risk of 32%. The sample size calculations were based on the primary intent-to-treat analysis in which the syncope-specific hazard function was used to estimate the treatment effect. A sample size of 310 patients provided an 85% power to detect a treatment effect with a hazard ratio (HR) of 0.64 for fludrocortisone compared with placebo, which is equivalent to a relative risk reduction of 40%, allowing for an anticipated 12.5% of the study sample lost to follow-up before a primary outcome event.

However, after several years, the enrollment rate dwindled, and this was refractory to changes in strategy and funding, which were also approaching exhaustion. This coincided with a planned interim analysis by a blinded data safety and monitoring committee. These analyses were planned for 6 months after 30% ($n = 93$) and 60% ($n = 186$) of the patients were enrolled, with termination if the analysis reached a $p < 0.001$ for benefit or $p < 0.01$ for harm with 2-tailed analyses. Blinded data were sent to the committee, which separately received the randomization key from the research pharmacy. The committee statistician did the interim analysis. The overall experimental type I error (α) was maintained at 5% using the O'Brien-Fleming design for a total of 3 tests with 2-sided significance levels of 0.0006, 0.0151, and 0.0472 to detect benefit.

An interim blinded analysis revealed a combined event rate of 50% per year, well above the anticipated combined rate of 32%. This led to a reduction in planned sample size to 208 patients. This had the power to detect an HR of 0.48 for treatment compared with placebo, equivalent to a relative risk reduction of 40% from 62.5% in the placebo arm to 37.5% in the treatment arm.

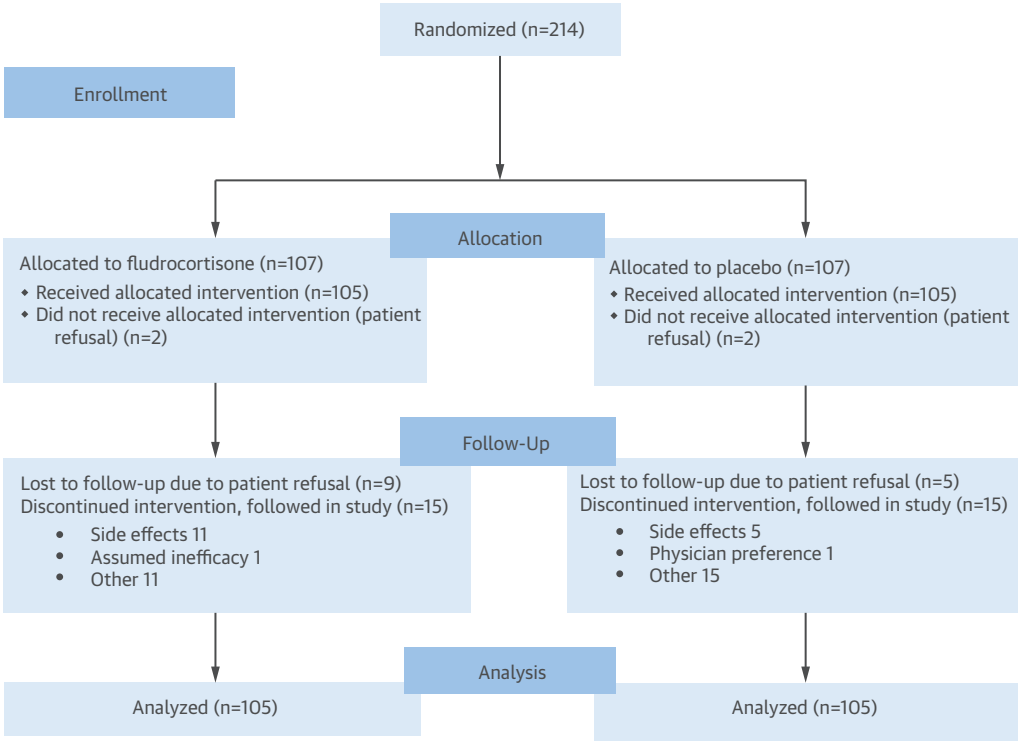
The University of Calgary Syncope Clinic coordinated the trial and managed data storage and analysis. All participants, investigators, and care providers were blinded throughout the study. Data were entered on paper case report forms and faxed to the coordinating center for entry into the database. The timing of the first recurrence of syncope was used as the primary outcome measure because it correlates well with the frequency of syncope, which in turn correlates with the diminution of quality of life in syncope patients (1,18). It also reflects the anticipated withdrawal rate based on our experience in the POST 1 (Prevention of Syncope Trial 1) (19). Syncope was verified within 1 week by recording the nature of the syncopal episode, collateral history from bystander witnesses, and examination of the patient for signs of physical trauma. A blinded outcomes adjudication committee adjudicated outcomes. Baseline characteristics are described as median and interquartile range (IQR) for continuous variables and percentages for categorical variables.

The primary analysis was on an intent-to-treat basis. Where possible, patients who withdrew from active treatment prematurely (such as treatment crossover, presumed side effects) were followed for the full year. Patients who were completely lost to follow-up before experiencing syncope or who actively withdrew prematurely without any follow-up were censored at the last observation time. Time to first syncope was described using the survivor function. The treatment effect was estimated using the syncope-specific HR, which is the HR estimated with complete withdrawals censored at the last observation time. We anticipated that some patients would be lost to follow-up after active withdrawal from treatment and provide no further information, which could constitute a competing risk (20); accordingly, we also performed a competing risks analysis.

A formal post hoc Cox proportional hazards regression model was conducted as specified in the protocol. Initially, each baseline variable was examined for a relationship with syncope recurrence, and the linearity assumption of each potential variable was examined using Martingale residuals and a natural logarithm transformation applied where necessary. Variables significant at $p < 0.2$ in the bivariable analysis were entered into the multivariable model, except for the number of spells in the previous year, due to collinearity with the lifetime frequency of syncopal episodes. Variables were removed backwards manually until all variables retained in the model were significant at $p < 0.05$ in a 2-tailed analyses. The proportional hazards assumption was examined using Schoenfeld residuals.

A secondary analysis was done in which syncope events in the initial dose-ranging period of 2 weeks were ignored but patients remained in the study. The rationale for this analysis was based on the fact that

FIGURE 1 Patient Flow



A total of 214 patients were randomized evenly to treatment with fludrocortisone or placebo. A total of 2 in each arm did not receive the allocated intervention, leaving 105 in each group for analysis.

treatment was initiated at a 0.1 mg dose of study drug daily with the intent to increase to 0.2 mg daily within 5 to 14 days. A number of subgroup analyses were performed in an exploratory manner to determine whether there might be specific groups of patients more likely to respond to treatment.

TABLE 1 Baseline Characteristics*

	Placebo (n = 105)	Fludrocortisone (n = 105)
Age, yrs	28 (21-44)	31 (23-47)
Females	75 (71)	71 (68)
BMI, kg/m^2	24.2 (21.6-27.5)	23.9 (21.7-28.9)
Syncope history		
Age of onset, yrs	17 (13-22)	16 (12-22)
Lifetime number of spells	15 (7-50)	20 (6-45)
Symptom duration, yrs	8 (2-23)	12 (4-21)
Syncope frequency, episodes/yr	2.5 (0.75-8)	2.1 (0.75-8)
Spells in previous year	4 (2-15)	3 (1-15)
Systolic blood pressure, mm Hg	112 (107-120)	113 (104-120)
Heart rate, beats/min	70 (62-78)	70 (64-78)

Values are median (interquartile range) or n (%). *The significance of any differences between randomization arms is not reported, in accordance with CONSORT guidelines (30).

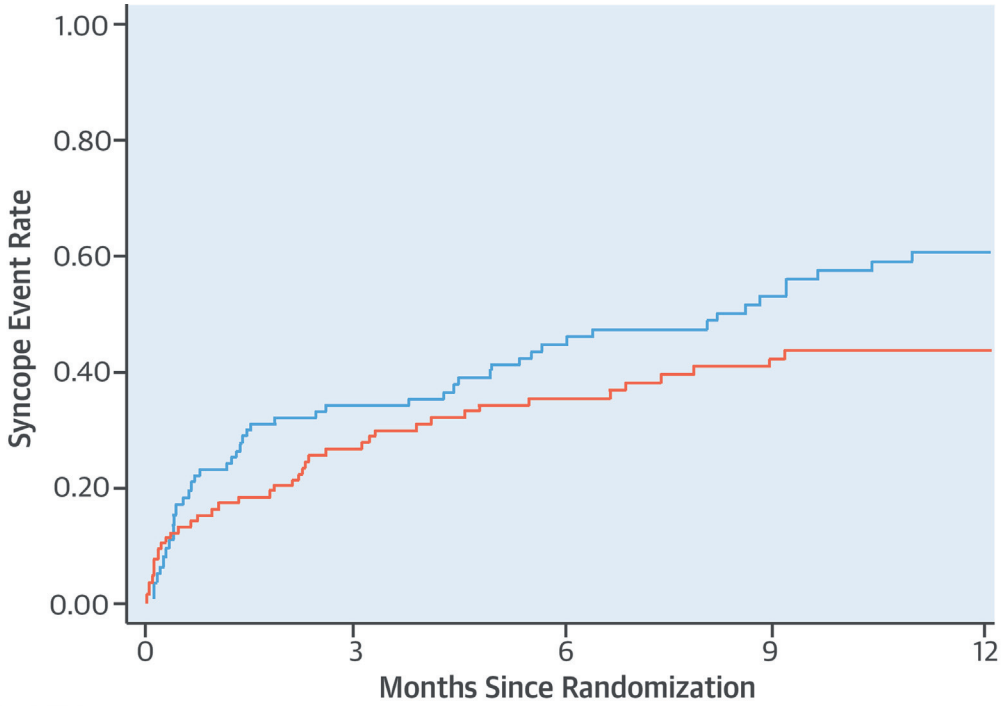
BMI = body mass index.

RESULTS

Between June 2005 and August 2010, 214 consenting patients were randomized in 17 university hospitals in Canada, Columbia, the United States, and Poland (Figure 1). Of these, 4 patients withdrew before ingesting the first pill, resulting in a study population of 210 subjects as planned following the interim analysis (Table 1). The median age was 30 years, 146 (70%) were women, and 16 patients were ages 15 to 17 years. Before randomization, study participants had a median 15 syncope spells over a median 9 years, with a median frequency of 2.3 syncopal episodes per year. They had a median 4 syncopal events in the year before randomization. The median supine heart rates and BP were 70 beats/min and 112/70 mm Hg, respectively.

The subjects in the fludrocortisone and placebo arms were followed for medians of 364 days (IQR: 187 to 365 days) and 364 days (IQR: 150 to 365 days),

CENTRAL ILLUSTRATION **Fludrocortisone Use in the Prevention in Vasovagal Syncope**



Patients at Risk

Placebo	105	62	44	32	25
Fludrocortisone	105	68	53	40	34

Placebo Fludrocortisone

Sheldon, R. et al. J Am Coll Cardiol. 2016;68(1):1–9.

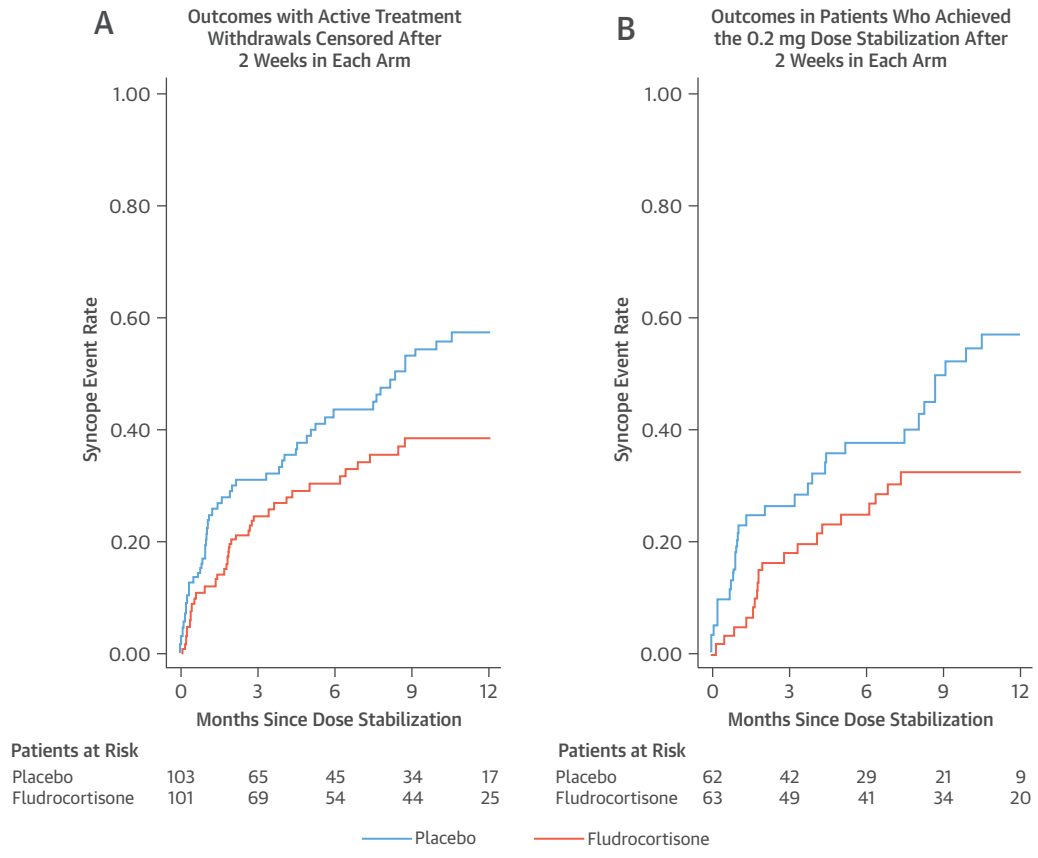
Use of fludrocortisone in vasovagal syncope is not well studied. Here, it was compared with placebo in patients with recurrent vasovagal syncope. In an intent-to-treat analysis, the 12-month syncope event rates were lower in the fludrocortisone arm compared with placebo (44.0% vs. 60.5%), but the difference was not statistically significant (p = 0.069).

respectively. A total of 96 patients had at least one syncopal spell, and 56 patients completed the study without syncope. Not all patients completed the study (**Figure 1**): 58 patients withdrew from follow-up before syncope (32 in the fludrocortisone arm and 26 in the control arm). Of these, 14 (6.7%) were simply lost to follow-up (9 in the fludrocortisone arm and 5 in the control arm), and the rest were followed in the study. The stated reasons for premature termination in the study by patients in the fludrocortisone group were presumed side effects (n = 11), presumed treatment failure (n = 1), and other reasons (n = 11 each), and in the placebo group were presumed side effects (n = 5), physician preference (n = 1), and other reasons (n = 15).

EFFECT OF FLUDROCORTISONE. In the intent-to-treat analysis, 42 of 105 subjects randomized to receive fludrocortisone had at least 1 syncopal spell, compared with 54 of 105 randomized to receive placebo. The 12-month syncope event rates in these 210 subjects (**Central Illustration**) were 44.0% and 60.5% on fludrocortisone and placebo, respectively (HR: 0.69; 95% confidence interval [CI]: 0.46 to 1.03; p = 0.069). In the competing risk analysis, the 12-month syncope event rate was 41% and 54.5% in the fludrocortisone and placebo arms, respectively (p = 0.082). Therefore, the study did not demonstrate its pre-specified relative risk reduction of 40% of the primary outcome. There were no serious adverse events.

EFFICACY ANALYSIS. Patients underwent 2-week dose stabilization with the intent of reaching 0.2 mg of fludrocortisone daily. Seven subjects fainted in

FIGURE 2 Dose Stabilization: Probability of First Syncope Episode



Dose stabilization (0.2 mg dose) was achieved in 61.3% of all patients 2 weeks after randomization. In total, 87 patients experienced a first syncope recurrence after 2 weeks: 35 in the fludrocortisone arm and 52 in the placebo arm **(A)**, a significant reduction per the exploratory analysis ($p = 0.029$). When analyzing only those patients who achieved the stabilized dose **(B)**, fludrocortisone again significantly reduced symptoms ($p = 0.019$).

the initial 2 weeks of dose stabilization; of these, 1 subject was lost to follow-up, and 6 were followed until study exit and included in this analysis. Additionally, 5 patients withdrew completely from the study and provided no data for this analysis, leaving 204 subjects. There was no significant difference between the treatment ($n = 101$) and placebo ($n = 103$) groups in the stabilized drug dose ($p = 0.96$).

Fully 61.3% of all patients reached the 0.2-mg dose 2 weeks after randomization. There were 87 patients with a first syncope recurrence after 2 weeks, 35 in the fludrocortisone arm and 52 in the placebo arm (Figure 2A). In this exploratory analysis, analyzing only syncopal spells occurring after the first 2 weeks, fludrocortisone significantly reduced the proportion of patients with syncope (HR: 0.62; 95% CI: 0.40 to 0.95; $p = 0.029$). When further restricted to patients who achieved a stabilized dose of 0.2 mg (Figure 2B), there was a significant reduction in symptoms due to treatment with fludrocortisone (HR: 0.51; 95% CI: 0.28 to 0.89; $p = 0.019$).

EXPLORATORY SUBGROUP ANALYSES. In a prespecified multivariable model that adjusted for the lifetime frequency of spells (Table 2), there was a significant reduction in syncope in the fludrocortisone group (HR: 0.63; 95% CI: 0.42 to 0.94; $p = 0.024$). Patients with a significant benefit in univariable analysis were those who had a baseline systolic BP <110 mm Hg (HR: 0.48; 95% CI: 0.25 to 0.92; $p = 0.028$), a body mass index ≥20 (HR: 0.59; 95% CI: 0.37 to 0.95; $p = 0.030$), syncope frequency ≥8 episodes/year (HR: 0.46; 95% CI: 0.23 to 0.95; $p = 0.036$); and those receiving fludrocortisone (HR: 0.63; 95% CI: 0.42 to 0.94; $p = 0.024$).

TABLE 2 Bivariable Proportional Hazards Regression

	Bivariable Analysis		
	HR Estimate	95% CI	p Value*
Treatment	−0.38	−0.78 to 0.030	0.069
Sex	0.70	0.22 to 1.19	0.005
Onset age, yrs	−0.0076	−0.0245 to 0.0092	0.375
Age at randomization, yrs	−0.022	−0.037 to −0.007	0.005
BMI	0.026	−0.005 to 0.058	0.100
Heart rate, beats/min	0.016	−0.0028 to 0.035	0.094
Systolic blood pressure, mm Hg	−0.003	−0.020 to 0.014	0.721
Episodes in last year, log	0.55	0.41 to 0.68	<0.001
Lifetime frequency of spells, log	0.34	0.24 to 0.45	<0.001

*Variables that remained significant in the multivariable model were (log) lifetime frequency of episodes (HR: 1.43; 95% CI: 1.28 to 1.60; $p < 0.001$) and treatment (HR: 0.63; 95% CI: 0.42 to 0.94; $p = 0.024$); after controlling for these 2 variables, none of the remaining variables were significant at $p < 0.05$.

BMI = body mass index; CI = confidence interval; HR = hazard ratio.

DISCUSSION

The major finding is that the study did not meet its primary objective of demonstrating that fludrocortisone reduce the likelihood of vasovagal syncope in patients with a history of numerous syncopal events by the specified risk reduction of 40%.

Proven effective treatments for vasovagal syncope remain elusive. Increased salt and fluid intake (17,21) is commonly advised, but unproven. Counterpressure maneuvers may be effective (16) but have not been tested in a blinded fashion. Midodrine was effective in 4 small studies (22), but none satisfied criteria for a pivotal clinical trial. The effectiveness of serotonin-specific reuptake inhibitors is uncertain (2), and permanent pacing may prevent syncope in patients with documented pauses during syncope, although it is unclear whether this is vasovagal syncope (3,23). Finally, although ineffective in young people, beta-blockers demonstrate some evidence of effectiveness in older patients (19,24). Given this, the finding that fludrocortisone significantly reduced the probability of syncope would have significantly improved patient care. The patients in this study were highly symptomatic, with a median of 3 to 4 faints in the year before randomization, and also resemble those who are most likely to request active biomedical treatment. Furthermore, they were defined using clinical criteria rather than tilt table testing, which should ease generalizability.

Vasovagal syncope is often preceded by orthostatic stress, and upright postures cause dependent pooling of up to 800 ml of venous blood. Patients with vasovagal syncope have ineffective venoconstrictive responses (25–27) and decreased venous return, which in turn decreases cardiac output, causing hypotension and, eventually, decreased cerebral perfusion (27). Ultimately, paradoxic vasodilation may occur (6,7), leading to further hypotension and loss of consciousness. Fludrocortisone increases renal sodium reabsorption, expands plasma volume, and has been a mainstay of treatment for orthostatic hypotension due to autonomic failure for decades (28). The evidence of effectiveness in adults with vasovagal syncope is lacking (9–11).

We tested the use of fludrocortisone in adults in a placebo-controlled, randomized clinical trial, targeting a maximum dose of 0.2 mg daily. The highest recommended dose in orthostatic hypotension is 0.3 mg daily (28), and we opted for a slightly lower dose to increase the margin of safety, given the lack of evidence of safety in its long-term use in young people. In the absence of preliminary data on which to base calculations, we powered the study around an international consensus that defined a minimum clinically important difference of 40%. In fact, we only detected an insignificant 31% reduction in the hazard of fainting in the formal intent-to-treat analysis ($p = 0.069$). To probe the possible source of this result, we performed a post hoc multivariable analysis and an on-treatment analysis; both showed a significant reduction in the likelihood of a syncope recurrence in subjects taking fludrocortisone. An exploratory analysis suggested that a daily dose of 0.2 mg should be targeted.

STUDY LIMITATIONS. The most important limitation is the low power provided by our initial assumptions. In the absence of data concerning the effect size of fludrocortisone, we canvassed international experts about a desirable effect size to commit a young patient to treatment with fludrocortisone. The mid-range desirable effect was a 40% relative risk reduction, and the study was powered around this a priori minimal clinically important difference. Indeed, the most significant findings were in the post hoc multivariable and on-treatment analyses. The sample was reduced after enrollments dwindled, funds became exhausted, and the data safety and monitoring committee determined that we would achieve our pre-specified number of outcomes with a smaller sample size. A second limitation is that the collection of study endpoints began before the final dose was achieved. Indeed, the study demonstrated a significant effect after dose stabilization. A wash-in blanking period is used when dose ranging or assessment of drug tolerance become necessary in study design (29), and does resemble the clinical reality of drug prescribing.

We included patients on the basis of a diagnostic score, which was developed using patients with tightly defined and documented causes of syncope, rather than tilt-table testing. This provided internal validity by encompassing a sample population on the basis of robust clinical criteria. The score based on settings and symptoms alone also provided a patient population that can be reproduced in other studies. The most desirable measure was syncope frequency, but the anticipated dropout rate discouraged inclusion of this measure as a primary outcome. However, both intervention arms had very similar observation durations, and the higher dose provided an important reduction in syncope number. Finally, a substantial minority of subjects withdrew from active treatment without having fainted. To address this, we confirmed the robustness of the conclusions with a competing risks analysis. Only a small minority (6.7%) of participants were completely lost to follow-up before a study outcome.

CONCLUSIONS

Although the study did not demonstrate that fludrocortisone reduced the likelihood of vasovagal syncope by the specified risk reduction of 40%, significant effects were noted after dose stabilization and in post hoc multivariable and on-treatment analyses. Larger studies would be needed to determine the agent's utility in specific subgroups of patients.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In a randomized trial, patients with vasovagal syncope improved only modestly after treatment with fludrocortisone 0.2 mg daily.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether specific clinical characteristics of patients with vasovagal syncope identify subgroups more or less likely to respond favorably to mineralocorticoid therapy.

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