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Quality of life improves in vasovagal syncope patients after clinical trial enrollment regardless of fainting in follow-up

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ABSTRACT

Background: Frequent syncope is linked to poorer health-related quality of life (HRQoL). Recurrent syncope has been observed to reduce in all groups after seeing a syncope expert and enrolling in a clinical trial. It is unknown if HRQoL improves with this reduction in syncope recurrence.
Objectives: We examined the change in HRQoL over time in vasovagal syncope (VVS) patients seen by a syncope expert and enrolled in a trial. We also explored whether change differed with treatment or the frequency of fainting during follow up.
Methods: The Short Form Health Survey (SF36) was completed at baseline (BL), 6 m, and 12 m post-enrollment by VVS patients in the 1st and 2nd Prevention of Syncope Trials, which were multi-centered, randomized, placebo-controlled trials of metoprolol (POST) and fludrocortisone (POST2). Differences in HRQoL at BL, 6 m, and 12 m were analyzed and compared by faints in follow-up and randomization group.
Results: Complete study data were available for 143 VVS patients (40 ± 17 years, 62% F). Over 12 months, patients reported improvement in all SF36 dimensions except for bodily pain. Post hoc analyses indicated that differences first occurred between BL and 6 m for all but general health. Fainting in follow-up or drug randomization group did not diminish the improvements. The baseline syncope burden was not different whether patients' HRQoL improved or not.
Conclusion: HRQoL of VVS patients improves over time after enrolling in a clinical trial, even with recurrent faints or randomization to placebo. Improvements may result from alternative factors, such as interaction with experts or patient adjustment.

1. Introduction

Vasovagal syncope (VVS) is very common in the general population. The estimated proportion of individuals with VVS by age 60 years is 37%, although many patients first present with VVS in adolescence and remain susceptible throughout their lifetime (Serletis et al., 2006). It has been reported that the degree of impairment in health-related quality of life (HRQoL) experienced by syncope patients is similar to that of patients with severe rheumatoid arthritis or chronic lower back pain (Linzer et al., 1991). Due to the recurrent nature of VVS, it is important to explore whether HRQoL changes over time.

In patients presenting with transient loss of consciousness from any cause, it has been observed that 1 year after presentation, HRQoL improved in almost half of the patients (van Dijk et al., 2007). Currently, only one study has reported shorter-term improvements (within 6 months) in select measures of HRQoL for VVS patients specifically (Baron-Esquivias et al., 2005). Despite these observations, it remains unclear whether improvements in HRQoL diminish, sustain, or continue to improve in the longer-term. Additionally, factors such as female gender, higher level of comorbidity, shorter duration of complaints, presyncope, and recurrent episodes are associated with poorer QoL (Baron-Esquivias et al., 2005; van Dijk et al., 2006). However, there are limited data indicating which factors are associated with long-term changes in HRQoL for VVS patients. It is also unclear how recent syncope burden is associated with HRQoL, compared to more remote or lifetime syncope burden.

We sought to examine the change in HRQoL over time in VVS patients seen by a syncope expert and enrolled in a clinical trial.

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Secondarily, we explored whether the change differed with treatment or fainting during study follow up, and whether improvement in HRQoL was associated with burden of syncope at baseline. We tested the hypothesis that HRQoL improves over time. Secondarily, we tested the hypotheses that patients who received placebo or fainted in follow up would also have a lower HRQoL, and blunted changes in HRQoL compared to those who did not. We also hypothesized that improvements in HRQoL are associated with a lower burden of syncope at baseline.

2. Methods

2.1. Participants

VVS patients in this study were enrolled in either the Prevention of Syncope Trial (POST) (Sheldon et al., 2003; Sheldon et al., 2006) or the Second Prevention of Syncope Trial (POST II) (Sheldon et al., 2016; Raj et al., 2006), which were multi-centered, randomized, placebo-controlled trials of metoprolol (POST) and fludrocortisone (POST II). All participants were recruited from syncope and arrhythmia clinics.

POST study patients were eligible for inclusion if they had a positive response to the tilt-test protocol and one or both of ≥3 lifetime syncopal spells prior to the tilt test, or ≥1 syncope recurrence within 6 months of a positive tilt test. All centers involved in the study used drug-free head-up tilt with or without subsequent isoproterenol infusion if the first stage was negative. Patients were excluded if they could not give informed consent; had other causes of syncope; had other non-cardiovascular or cardiovascular diseases, or a permanent pacemaker; had a diagnosis of carotid sinus hypersensitivity; had a contraindication to, a pressing need for, or previously used β-blockers for the treatment of syncope.

POST II study patients were eligible for inclusion into the study if they were ≥14 years of age, had a score of ≥ −2 on the Calgary Syncope Symptom Score, and had ≥3 syncopal spells before enrollment. Patients were excluded if they could not give informed consent; had other causes of syncope; had other non-cardiovascular or cardiovascular diseases, or a permanent pacemaker, glaucoma, diabetes mellitus, hepatic or renal disease, a seizure disorder, or hypertension; had a contraindication to, a pressing need for, or had previously used fludrocortisone for the treatment of syncope. They were also excluded if they had indication of postural tachycardia (heart rate increase ≥ 30 beats/min) or orthostatic hypotension (BP decrease ≥ 20/10 mm Hg) during a 5-minute stand test.

Both POST and POST II were approved by the Conjoint Health Research Ethics Board for the Calgary site and the coordinating center, and by the local Ethics Boards for each site. Each individual has written informed consent to participate.

2.2. Surveys

VVS patients completed the Medical Outcomes Study Short Form-36 (SF36) at baseline, 6 months, and 12 months post-enrollment.

The SF36 is a widely used HRQoL survey composed of 36 items extracted from the Medical Outcomes Study (Hays and Morales, 2001). It assesses 8 health concepts with multi-item scales, which include physical functioning, role limitations due to physical health, role limitations due to emotional problems, social functioning, emotional well-being, energy or fatigue, pain, and general health. Role limitations refer to limitations in a participant's life, such as the ability to work, perform housework, schoolwork, or be involved in the community.

The scale scores range from 0 to 100, with higher scores indicating greater levels of functioning and a more favourable health state (Hays et al., 1993). Each scale score represents the average of all the items in the scale answered by the individual (Hays et al., 1993).

2.3. Statistical analysis

Demographic and clinical information are expressed as percentages for categorical data, mean (SD) for normally distributed continuous variables, and median (interquartile range [IQR], 25th percentile, 75th percentile) for non-normally distributed continuous variables. Categorical demographic variables were compared using the Fisher's exact test. Continuous demographic variables were assessed with the Student's *t*-test (normally distributed) or Mann-Whitney *U* test (non-normally distributed).

In both POST and POST II, a number of patients either withdrew or were lost to follow up prior to 12 months. Reasons for premature withdrawal included presumed side effects such as fatigue, presyncope, nausea, insomnia, and depression (Sheldon et al., 2006; Sheldon et al., 2016). To account for these possible differences, we compared patient demographics and clinical data between the entire study population and those who completed the study. The analyses of HRQoL over time focused on patients who completed the study.

Baseline, 6 month, and 12 month scale scores for the SF36 were calculated according to their respective scoring guidelines, and expressed as mean (SD). To examine the change in HRQoL over time, SF36 health-dimension scores at baseline, 6 months and 12 months post-enrollment were compared using repeated-measures ANOVA. Fainting status (whether the patient reported to have fainted during study follow up or not) and randomization (whether the patient received active drug or placebo) variables were added to the model individually, in order to examine their potential interactions with time. Post-hoc analyses were applied to observe where and when the significant differences in QoL occurred. p values were adjusted for multiple comparisons using the Bonferroni correction method, and were directly compared with a corrected alpha of 0.05. Additionally, QoL measures at each time point were stratified according to fainting status and randomization, and examined using the Mann Whitney *U* test.

Recent syncope burden was defined by the number of faints experienced in the 12 month follow up period, and categorized as having 1 faint, or > 1 faint. The differences in QoL at 12 months between groups were analyzed using the Student's *t*-test. Prior syncope burden was defined by both total lifetime episodes and episodes experienced in the year prior to enrollment. Differences in prior syncope burden were determined for patients who experienced a recurrent faint during follow up compared to those who did not, using a Mann Whitney *U* test.

Lastly, patients were also grouped according to whether they experienced an improvement in QoL at 12 months or not. Improvement was identified as having a change in SF36 scale scores of > 0, whereas no improvement was identified as having a change in SF36 scale scores of ≤0. Burden of syncope at baseline was analyzed for both groups. The number of lifetime faints and faints in the year prior to enrollment were log-transformed to account for skewed distributions.

All p-values were two-tailed and the statistical significance was set at $p < 0.05$. The analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY, USA). Figures were made using GraphPad Prism version 7.01 (GraphPad Software, La Jolla, CA, USA).

3. Results

3.1. Demographics

Completed survey data were available for 143 study participants. There were no significant differences at baseline between the entire study population and those who completed the study (Table 1). The mean age of the sample with complete data was 40 ± 17 years, and 62% were female. Prior to study enrollment, VVS patients had experienced a median of 10 (IQR 5, 20) lifetime syncope episodes over a median of 14 (IQR 5, 29) years. They reported a median of 3 (IQR 1, 6) syncopal episodes in the year prior to enrollment. During study follow-

Table 1
Baseline demographics for all VVS patients and patients who completed the study.

Parameter	All VVS	Completed study
Patients (n)	280	143
Age years, mean ± SD	39 ± 17	40 ± 17
Females (%)	65	62
Onset age years, mean ± SD	22 ± 17	22 ± 17
Faints in lifetime, median (IQR)	10 (5, 30)	10 (5, 20)
Faints in past year, median (IQR)	3 (1,6)	3 (1,6)
Fainted during follow up, n (%)	107 (38)	56 (40)
Randomization to active drug, n (%)	142 (51)	70 (49)

Table 2
Baseline SF36 scale scores between all VVS patients and patients who completed the study.

Scale	All VVS (n = 280)	Completed study (n = 143)	p value
Mental health	67 ± 20	70 ± 19	0.16
Role limitations (emotional)	72 ± 38	74 ± 38	0.62
Vitality	50 ± 22	53 ± 23	0.19
Social functioning	71 ± 27	76 ± 25	0.15
Physical functioning	78 ± 23	80 ± 24	0.58
Role limitations (physical)	59 ± 40	65 ± 40	0.15
General health	64 ± 22	66 ± 24	0.47
Bodily pain	67 ± 25	71 ± 24	0.17

up, 40% of patients reported that they experienced an episode of syncope during study follow up. Of these patients, 30 (54%) had 1 spell, 18 (32%) had 2–5 spells, and 8 (14%) had ≥6 spells.

3.2. Health-related quality of life

At baseline, there were no significant differences in any of the 8 health dimensions measured by the SF36 between all VVS patients and the subgroup of VVS patients who completed the study (Table 2).

For the dimensions related to mental health, there were significant improvements in mental health ($p < 0.001$), role limitations due to emotional health ($p = 0.003$), vitality ($p < 0.001$), and social functioning ($p = 0.001$) between baseline, 6 months, and 12 months of follow up (Table 3). Similarly, for the dimensions related to physical health, there were significant improvements in physical functioning ($p = 0.012$), role limitations due to physical health ($p = 0.007$), and general health ($p = 0.037$) between the 3 time points. There was no reported change in bodily pain ($p = 0.334$).

Post-hoc analyses further revealed that significant increases in the scales of mental health ($p < 0.001$), role limitations due to emotional health ($p = 0.009$), vitality ($p = 0.013$), and social functioning ($p = 0.017$) occurred between baseline and 6 months (Fig. 1). For the dimensions related to physical health, significant increases were found

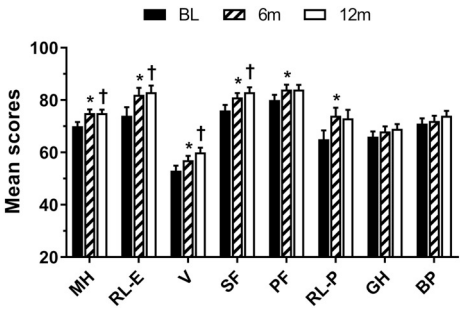

Fig. 1. Mean SF36 health dimension scores over time.
Higher scores in each scale indicate greater levels of functioning and a more favourable health state. There was improvement in all HRQoL measures, except for general health and bodily pain, from baseline to 6 months. There was reported improvement in all HRQoL measures related to mental health from baseline to 12 months, but no significant differences were observed in physical health measures. There were no significant differences in any of the SF36 scores between 6 and 12 months. MH – mental health; RL-E – role limitations due to emotional health; V – vitality; SF – social functioning; PF – physical functioning; RL-P – role limitations due to physical health; GH – general health; BP – bodily pain. * indicates $p < 0.05$ for BL to 6 months; † indicates $p < 0.05$ for BL to 12 months.

between baseline and 6 months for physical functioning ($p = 0.035$) and role limitations due to physical health ($p = 0.009$), but not for general health ($p = 0.302$). Additionally, there was an increase in all of the dimensions related to mental health between baseline and 12 months. For the dimensions related to physical health, there was a trend towards improvement between baseline and 12 months for physical functioning, role limitations due to physical health and general health, although none were statistically significant. No significant differences were observed in any of the SF36 scores between 6 and 12 months of follow up.

3.2.1. Presence of fainting during study follow up

VVS patients who had a recurrent faint during the follow up period had lower mean scores in all SF36 health dimensions at baseline compared to patients who did not faint; however, the differences were not statistically significant (Fig. 2A). At 12 months, patients with a recurrent faint reported significantly poorer scores in 5 of the 8 SF36 health dimensions compared to those who did not faint. They reported poorer general health ($p = 0.016$), less physical functioning ($p = 0.019$) and social functioning ($p = 0.04$), greater role limitations due to physical health ($p = 0.01$), and more bodily pain ($p = 0.006$) (Fig. 2B).

However, fainting during study follow up did not have a significant effect on the changes in HRQoL over time (Table 4; Fig. 3A). There was an observed overall improvement in all 8 of the SF36 health dimensions from baseline to 12 months, independent of whether patients experienced syncope recurrence. Therefore, patients with a recurrent faint started with a lower QoL and continued to fare worse at 12 months

Table 3
SF36 scores at baseline, 6 months, and 12 months for VVS patients who completed the study.

Scale	BL	6 m	12 m	ANOVA p value	BL vs 6 m p value	BL vs 12 m p value
Mental health	70 ± 19	75 ± 17	75 ± 16	< 0.001	< 0.001	< 0.001
Role limitations (emotional)	74 ± 38	82 ± 31	83 ± 30	0.003	0.009	0.033
Vitality	53 ± 23	57 ± 20	60 ± 21	< 0.001	0.013	0.001
Social functioning	76 ± 25	81 ± 21	83 ± 22	0.001	0.017	0.004
Physical functioning	80 ± 24	84 ± 22	84 ± 21	0.012	0.035	0.073
Role limitations (physical)	65 ± 40	74 ± 36	74 ± 38	0.007	0.009	0.066
General health	66 ± 24	68 ± 23	69 ± 21	0.037	0.302	0.056
Bodily pain	71 ± 24	72 ± 24	74 ± 22	0.334	1.000	0.487

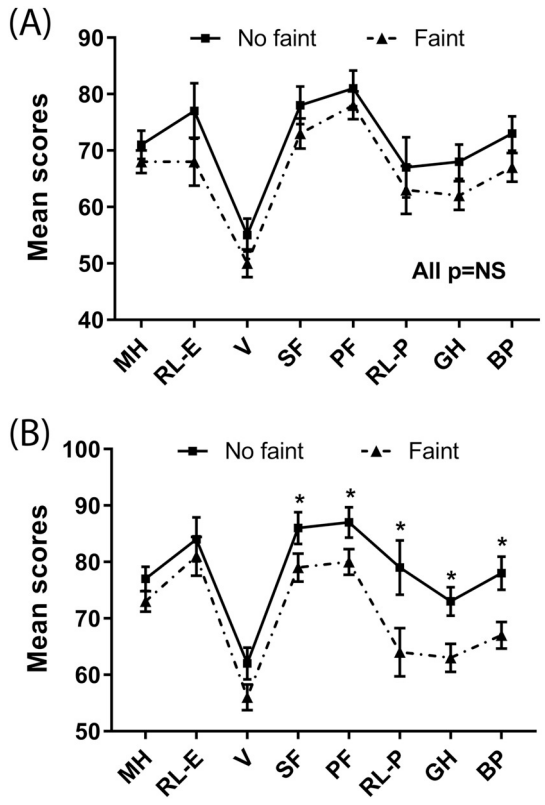

Fig. 2. Mean SF36 health dimensions scores at baseline and 12 months for patients who fainted during follow up compared to those who did not.
A) VVS patients who had a recurrent faint during the follow up period had lower mean scores in all SF36 health dimensions at baseline compared to patients who did not faint, although not significant. B) At 12 months, VVS patients who reported fainting during study follow up had poorer scores in 5 of the 8 health dimensions measured by the SF36 compared to those who did not faint. * indicates $p < 0.05$.

Table 4
SF36 scores at baseline, 6 months, and 12 months by fainting during follow up.

Scale	Status	Baseline	6 months	12 months	p value
Mental health	No faint	71 ± 19	76 ± 17	77 ± 16	0.975
	Faint	68 ± 19	73 ± 17	73 ± 17	
Role limitations (emotional)	No faint	77 ± 37	83 ± 30	84 ± 29	0.337
	Faint	68 ± 40	82 ± 33	81 ± 32	
Vitality	No faint	55 ± 22	59 ± 20	62 ± 21	0.965
	Faint	50 ± 23	55 ± 19	56 ± 21	
Social functioning	No faint	78 ± 25	85 ± 19	86 ± 21	0.705
	Faint	73 ± 25	77 ± 21	79 ± 23	
Physical functioning	No faint	81 ± 24	85 ± 22	87 ± 20	0.485
	Faint	78 ± 23	81 ± 20	80 ± 21	
Role limitations (physical)	No faint	67 ± 40	77 ± 35	79 ± 36	0.247
	Faint	63 ± 40	70 ± 38	64 ± 40	
General health	No faint	68 ± 23	71 ± 22	73 ± 19	0.378
	Faint	62 ± 24	63 ± 23	63 ± 23	
Bodily pain	No faint	73 ± 23	74 ± 24	78 ± 22	0.393
	Faint	67 ± 24	70 ± 25	67 ± 22	

compared to those who did not faint, despite improving a similar amount.

3.2.2. Burden of fainting during study follow up

There were no significant differences in any of the SF36 health dimensions at 12 months between patients who reported 1 faint during study follow up compared to those who reported > 1 faint. VVS patients with a recurrent faint during study follow up reported more

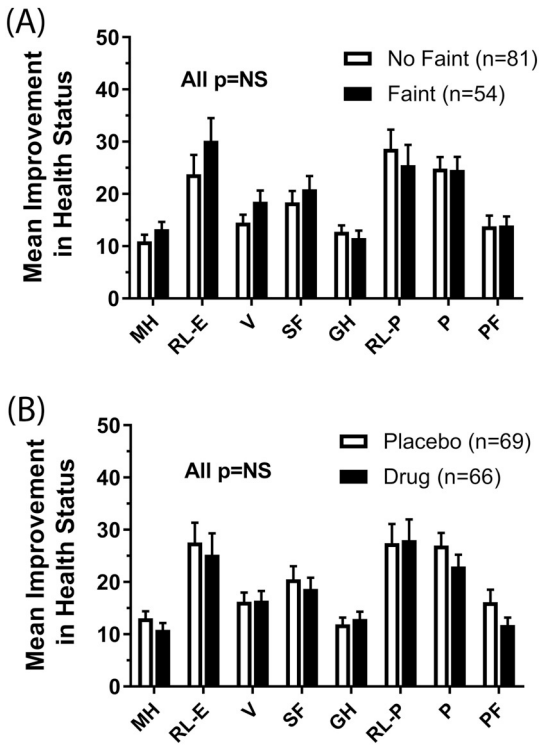

Fig. 3. Mean improvement in health status between baseline and 12 months stratified by fainting status and randomization.
There were no significant differences in mean delta values between baseline and 12 month SF36 scores when stratified by fainting status (A) and drug randomization (B).

syncope episodes in the year prior to enrollment compared to patients without a recurrent faint (4 (2, 10) vs 2 (1, 4); p = 0.002). However, there were no differences between groups in the number of total lifetime syncope episodes experienced (10 (5, 50) vs 10 (5, 16); p = 0.073).

3.2.3. Randomization to active drug or placebo

VVS patients who received active drug did not have significant differences in any of the 8 SF36 health dimensions at baseline, 6 months, and 12 months compared to patients who received placebo. Moreover, randomization to either active drug or placebo also did not affect any of the changes observed between the 3 time points (Table 5) (Fig. 3B). All SF36 scales improved from baseline to 12 months independent of the type of drug received.

3.2.4. Improvement in QoL and baseline syncope burden

From baseline to 12 months, improvement in HRQoL was observed in each of the 8 SF36 health dimensions, ranging from 30 to 55% of the VVS patients (Fig. 4). Vitality and mental health saw the largest numbers of patients experiencing improvement, with 55% and 52% of all patients, respectively. Of those who reported no improvement at 12 months, they were distributed between having experienced no change in QoL or a worsening in their QoL. Patients who improved were not significantly different in sex or age compared to those who experienced no improvement. There were also no significant differences between groups in the number of log lifetime faints or log faints in the year prior to enrollment (Table 6).

4. Discussion

The findings from this study demonstrate overall improvements in most HRQoL scales of the SF36 for patients with VVS, after enrolling in

Table 5
SF36 scores at baseline, 6 months, and 12 months by randomization.

Scale	Status	Baseline	6 months	12 months	p value
Mental health	Placebo	68 ± 19	75 ± 16	75 ± 15	0.109
	Drug	71 ± 19	74 ± 18	75 ± 18	
Role limitations (emotional)	Placebo	72 ± 38	87 ± 25	87 ± 22	0.087
	Drug	75 ± 38	78 ± 36	79 ± 36	
Vitality	Placebo	52 ± 23	58 ± 19	60 ± 20	0.331
	Drug	55 ± 22	57 ± 21	59 ± 22	
Social functioning	Placebo	76 ± 26	82 ± 19	83 ± 20	0.956
	Drug	76 ± 24	81 ± 22	84 ± 24	
Physical functioning	Placebo	80 ± 25	84 ± 20	84 ± 20	0.991
	Drug	79 ± 23	84 ± 23	84 ± 22	
Role limitations (physical)	Placebo	63 ± 41	71 ± 38	71 ± 38	0.824
	Drug	67 ± 39	78 ± 33	75 ± 39	
General health	Placebo	66 ± 25	69 ± 21	69 ± 20	0.744
	Drug	66 ± 23	67 ± 24	69 ± 23	
Bodily pain	Placebo	71 ± 23	73 ± 24	75 ± 20	0.890
	Drug	70 ± 25	72 ± 25	72 ± 24	

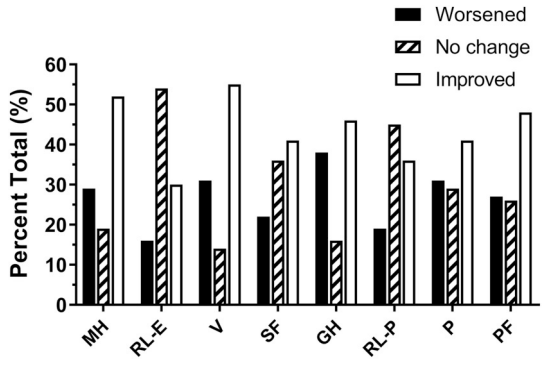

Fig. 4. VVS patients who reported improvement or not in SF36 scores from baseline to 12 months.
Percentage of all VVS patients who reported lower (worse), no change, or improvement in each SF36 scale from baseline to 12 months.

Table 6
Log baseline burden of syncope in patients who improved in HRQoL or not.

Scale	No improvement	Improved	p value
Lifetime faints			
Mental health	2.4 ± 0.13	2.8 ± 0.17	0.071
Role limitations (emotional)	2.4 ± 0.13	2.9 ± 0.20	0.046
Vitality	2.5 ± 0.16	2.6 ± 0.15	0.392
Social functioning	2.5 ± 0.14	2.6 ± 0.17	0.687
Physical functioning	2.4 ± 0.13	2.8 ± 0.17	0.097
Role limitations (physical)	2.5 ± 0.12	2.7 ± 0.21	0.220
General health	2.4 ± 0.13	2.8 ± 0.18	0.097
Bodily pain	2.6 ± 0.14	2.6 ± 0.17	0.921
Faints in the last year			
Mental health	1.2 ± 0.88	1.3 ± 1.2	0.571
Role limitations (emotional)	1.1 ± 1.0	1.5 ± 1.2	0.122
Vitality	1.1 ± 0.93	1.3 ± 1.2	0.333
Social functioning	1.2 ± 1.1	1.3 ± 1.1	0.829
Physical functioning	1.2 ± 1.0	1.2 ± 1.1	0.850
Role limitations (physical)	1.1 ± 1.0	1.4 ± 1.1	0.269
General health	1.1 ± 1.0	1.3 ± 1.1	0.339
Bodily pain	1.2 ± 1.0	1.2 ± 1.1	0.990

and completing a clinical trial. These improvements predominantly occur in the shorter term and then remain sustained in the longer term. As well, the changes occur independently of syncope recurrence or randomization to placebo or active medication. Furthermore, baseline burden of syncope did not differ significantly between patients who improved compared to patients who did not.

4.1. Changes in HRQoL over time

HRQoL was observed to improve over time in VVS patients. Our results indicate that the most significant changes can occur within 6 months of enrollment into a clinical trial and then remain sustained at 12 months. This is consistent with previous findings that have identified improvement in select measures of HRQoL at 6 months (Baron-Esquivias et al., 2005), and our study extends these findings out to 12 months after enrollment. We also found significant improvement in 6 of the 8 health dimensions of the SF36 within 6 months of follow up, compared to only 3 dimensions in the previous study. Although both study populations were similar in sample size, sex, and age, patients in the previous study were not involved in a randomized controlled trial, which could be a possible factor contributing to the differences observed. Interestingly, of the dimensions that showed improvement, a discrepancy between the studies was in general health. The prior study found significant improvement at 6 months whereas our current study did not. Future initiatives to validate and better understand this dimension in VVS patients may be beneficial. Furthermore, bodily pain did not improve in either studies, which may indicate a dimension of HRQoL that is more resistant to change in VVS patients, and therefore may require greater attention in follow up. Another explanation may be that bodily pain is not associated with syncope other than as a cause. Further research may be required to confirm the reasons behind this observation.

Additionally, while others have reported improvement in HRQoL after 1 year in patients presenting with TLOC (van Dijk et al., 2007), similar findings have not been previously reported in a VVS population. The patients in our study were also more symptomatic, with a median lifetime number of 10 faints compared to 3 faints in the prior study. Despite this, both study populations improved a similar amount, indicating that factors other than syncope recurrence may be associated with changes in QoL. Moreover, although the HRQoL dimensions related to mental health are observed to significantly improve in the longer term, the dimensions related to physical health do not. For select measures, such as physical functioning and role limitations due to physical health, this occurs despite an initial transient improvement at 6 months. Confirmation of these results and identification of the reasons behind this discrepancy warrant further research. It would also be of interest to observe whether the implementation of additional interventions such as physical therapy may help to sustain these dimensions in the longer term.

It was also observed that despite improvement over time, VVS patients scored consistently lower in the vitality subscale compared to other health dimensions, including physical functioning, mental health, and general health. This finding is interesting as it may suggest that VVS patients do relatively well in general, but feel worn out from stress, treatment, the condition, or a combination of all. Future studies measuring HRQoL in VVS patients could benefit from a more in depth analysis of the reasons underlying these feelings.

Lastly, while our results show a clear statistical difference in mean SF36 scores over time, it remains unclear how much change might constitute a clinically relevant change in VVS patients specifically. This calls for further investigation, and may require insight from both clinicians and patients. We also observed that some patients improved, some noted no change, and some fared worse. Our results indicated that neither sex, age, nor prior burden of syncope were different between groups. Other possible predictors may include social and environmental factors experienced by the individual, and these should be explored in future studies.

4.2. Effect of recurrent faints on changes in HRQoL

VVS patients who fainted during study follow up reported poorer scores in 5 of the 8 SF36 health dimensions at 12 months compared to those who did not faint. Despite this, both groups experienced an

improvement in HRQoL within the 12 months. These findings differ from previously published data, which found that VVS patients with syncope recurrence experienced an overall worsening in their quality of life compared to those who did not (Baron-Esquivias et al., 2005). The prior study, however, had a shorter follow up period of 6 months, and a lower syncope recurrence rate (20% vs 40%) compared to the current study.

Our findings suggest that patients who experience recent syncope recurrence have a lower HRQoL compared to those who do not, and the negative association occurs independent of the total number of lifetime faints. Additionally, HRQoL does not differ between patients who only faint once in follow up compared to those who faint more than once. Interestingly, previous studies have reported that patients with longer periods of TLOC show better mental functioning and disease-specific QoL compared to those with a recent onset of symptoms (van Dijk et al., 2006). Therefore, recent syncope recurrence may also be an indicator of poor HRQoL in VVS patients; however, the actual number of events experienced may be less relevant. Moreover, although patients who faint during study follow up may require greater attention by treating physicians for their comparably poorer QoL, syncope recurrence is likely not the sole determinant for short-term and long-term improvement. For example, it is possible that patients are able to adapt to recurrent episodes of syncope over time (van Dijk et al., 2006). There have also been prior suggestions that improvements in syncope recurrence are associated with expectations attached to the syncope "expert" (Sahota et al., 2014). Patients seem to fare better after being seen in specialty clinics or involved in clinical trials. It may be of interest to observe whether improvements in HRQoL are associated with the strength of the physician-patient relationship in a similar manner.

4.3. Effect of treatment on changes in HRQoL

Randomization to either active drug or placebo did not have an effect on the HRQoL of patients at baseline, 6 months or 12 months. These results are consistent with the non-significant effects of metoprolol and fludrocortisone on syncope recurrence in the POST and POST II studies, respectively (Sheldon et al., 2006; Sheldon et al., 2016). However, an important finding in this study is that randomization also did not have an effect on the change in HRQoL over time; both groups were observed to improve over the 12 months study period independent of study drug versus placebo.

Previous findings from the POST study also found no demonstrable effect of metoprolol on the quality of life of VVS patients at 6 and 12 months of treatment, as measured by the EQ-5D (Sheldon et al., 2009). Furthermore, there was no significant benefit in QoL measured by either the SF36 physical domain or SF36 mental health domain after 6 and 12 months of treatment in patients who completed follow up. Despite these results, the study had a small sample size and consisted largely of middle-aged individuals. Patients enrolled in POST II were younger in comparison (median age of 30 years) (Sheldon et al., 2016), and therefore by pooling POST and POST II data, we were able to generate a bigger sample size and examine patients within a larger age range. This also helped to reduce the drug effect, due to the known side effects associated with beta-blockers. Using the same measurement tools then allowed us to confirm and extend these previously reported findings.

Interestingly, when stratified by age, beta-blocker treatment was found to have an age-dependent effect in VVS patients, with older patients experiencing a greater reduction in the risk of syncope recurrence (Sheldon et al., 2012). However, there was no corresponding improvement in QoL associated with metoprolol in patients either < 42 or ≥ 42 years of age (Sheldon et al., 2009). This, along with our current findings, suggests that factors other than syncope recurrence and treatment are likely to be involved with changes in QoL over time.

4.4. Clinical implications

Patient reported outcomes such as HRQoL can provide important information regarding the impact of disease on day-to-day living. Due to the chronic and recurrent nature of VVS, understanding how HRQoL changes over time can enable clinicians to better monitor patients under their care. Moreover, identifying the clinical factors that are associated with these changes can serve to help in the recognition of patients who require greater support. It is also possible that improvements in HRQoL may result from alternative factors, such as the interaction and reassurance from expert physicians during follow up, or simply patient adjustment over time. Overall, this knowledge can aid in the development of more personalized treatment plans during presentation and in subsequent follow up visits.

4.5. Study limitations

The data that were collected in this study were subjective, self-reported measures of HRQoL, which may be open to bias and misinterpretation. However, the tools used are both common and well validated, which should have minimized this risk and increased the reliability of the data. As well, a potential limitation associated with the SF-36 is the possibility of a ceiling effect that can interfere with capturing clinically important changes over time. For example, if a high proportion of individuals reported the maximum score on a given health dimension at baseline, they would not have been able to report a score higher than the maximal score in follow-up. Consequently, even if improvement occurs during the study, the scale may not be responsive to their change. This issue may be of interest for further exploration in future studies of VVS.

This study also evaluated symptomatic patients with recurrent episodes, all of whom were referred to syncope or arrhythmia clinics. It is therefore possible that these patients are not fully representative of all individuals with syncope, and may represent those who are more willing to seek help, or those who have poorer health. Additionally, the data focused on VVS patients who completed the study. There were high rates of attrition in the number of individuals that remained in the study for the 12-month follow up period. As such, these results might not be generalizable to all VVS patients who enter a clinical trial. It is also possible that those who withdrew or were lost to follow up may have had a worsening HRQoL, and therefore were less motivated to continue. We are unable to assume that they would have had the same HRQoL trajectories as those who remained in the study.

Furthermore, although we are able to identify that syncope recurrence and treatment did not significantly affect the improvement in HRQoL over time, it remains undetermined what factors do contribute to the observed improvements. Lastly, while one possible factor is the interaction with a syncope expert, there was no control group in our study with care provided by non-expert staff. Future studies are required to validate this as a potential factor.

5. Conclusions

HRQoL of VVS patients improves over time after enrolling in a clinical trial and seeing an expert, even with recurrent faints or randomization to placebo. Furthermore, these changes occur within the first 6 months, and in many cases are sustained for at least a year. Future studies should aim to identify how psychological distress in VVS patients continues to change over the long term, as well as which specific factors such as syncope recurrence or specific therapies are associated with the changes.

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References

Baron-Esquivias, G., Gomez, S., Aguilera, A., Campos, A., Romero, N., Cayuela, A., Valle, J.I., Redondo, M., Pedrote, A., Burgos, J., Martinez, A., Errazquin, F., 2005. Short-term evolution of vasovagal syncope: influence on the quality of life. Int J Cardiol. 102, 315–319.

van Dijk, N., Sprangers, M.A., Colman, N., Boer, K.R., Wieling, W., Linzer, M., 2006. Clinical factors associated with quality of life in patients with transient loss of consciousness. J Cardiovasc Electrophysiol. 17, 998–1003.

van Dijk, N., Sprangers, M.A., Boer, K.R., Colman, N., Wieling, W., Linzer, M., 2007. Quality of life within one year following presentation after transient loss of consciousness. Am J Cardiol. 100, 672–676.

Hays, R.D., Morales, L.S., 2001. The RAND-36 measure of health-related quality of life. Ann Med. 33, 350–357.

Hays, R.D., Sherbourne, C.D., Mazel, R.M., 1993. The RAND 36-Item Health Survey 1.0. Health Econ. 2, 217–227.

Linzer, M., Pontinen, M., Gold, D.T., Divine, G.W., Felder, A., Brooks, W.B., 1991. Impairment of physical and psychosocial function in recurrent syncope. J Clin Epidemiol. 44, 1037–1043.

Raj SR, Rose S, Ritchie D, Sheldon RS and Investigators PI. The Second Prevention of Syncope Trial (POST II)—a randomized clinical trial of fludrocortisone for the prevention of neurally mediated syncope: rationale and study design. Am Heart J. 2006;151:1186 e11-7.

Sahota, I., Sheldon, R., Pournazari, P., 2014. Clinical improvement of vasovagal syncope in the absence of specific therapies: the Seinfeld effect. Cardiol J. 21, 637–642.

Serletis, A., Rose, S., Sheldon, A.G., Sheldon, R.S., 2006. Vasovagal syncope in medical students and their first-degree relatives. Eur Heart J. 27, 1965–1970.

Sheldon, R., Rose, S., Connolly, S., 2003. Prevention of Syncope Trial (POST): a randomized clinical trial of beta blockers in the prevention of vasovagal syncope; rationale and study design. Europace. 5, 71–75.

Sheldon, R., Connolly, S., Rose, S., Klingenheben, T., Krahn, A., Morillo, C., Talajic, M., Ku, T., Fouad-Tarazi, F., Ritchie, D., Koshman, M.L., Investigators, P., 2006. Prevention of Syncope Trial (POST): a randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. Circulation. 113, 1164–1170.

Sheldon, R.S., Amuah, J.E., Connolly, S.J., Rose, S., Morillo, C.A., Talajic, M., Kus, T., Fouad-Tarazi, F., Klingenheben, T., Krahn, A.D., Koshman, M.L., Ritchie, D., Prevention of Syncope T, 2009. Effect of metoprolol on quality of life in the Prevention of Syncope Trial. J Cardiovasc Electrophysiol. 20, 1083–1088.

Sheldon, R.S., Morillo, C.A., Klingenheben, T., Krahn, A.D., Sheldon, A., Rose, M.S., 2012. Age-dependent effect of beta-blockers in preventing vasovagal syncope. Circ Arrhythm Electrophysiol. 5, 920–926.

Sheldon, R., Raj, S.R., Rose, M.S., Morillo, C.A., Krahn, A.D., Medina, E., Talajic, M., Kus, T., Seifer, C.M., Lelonek, M., Klingenheben, T., Parkash, R., Ritchie, D., McRae, M., Investigators, P., 2016. Fludrocortisone for the prevention of vasovagal syncope: a randomized, placebo-controlled trial. J Am Coll Cardiol. 68, 1–9.