Neurally-mediated reflex syncope: diagnosis and treatment
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Chapter 4

Prospective evaluation of non-pharmacological treatment in vasovagal syncope

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Abstract

Aims: Initial treatment of vasovagal syncope (VVS) consists of assuring an adequate fluid and salt intake, regular exercise and application of physical counterpressure manoeuvres. We examined the effects of this non-pharmacological treatment in patients with frequent recurrences.

Methods: One hundred patients with ≥3 episodes of VVS in the 2 years prior to the start of the study openly received non-pharmacological treatment. We evaluated this treatment both with respect to syncopal recurrences, factors associated with recurrence, and quality of life (QoL).

Results: The median number of syncopal recurrences was lower in the first year of non-pharmacological treatment compared with the last year before treatment (median 0 vs. 3; \(P < 0.001\)), but 49% of patients experienced at least one recurrence. In multivariable analysis, a higher syncope burden prior to inclusion was significantly associated with syncopal recurrence. Disease-specific QoL improved over time, with larger improvements for patients with more reduction in syncope burden.

Conclusion: In patients with frequent recurrences of VVS, non-pharmacological treatment has a beneficial effect on both syncopal recurrence and QoL, but nearly half of these patients still experience episodes of syncope.
Introduction

Syncope is a self-limited episode of transient loss of consciousness (T-LOC) due to a transient hypoperfusion of the brain. Reflex syncope is caused by systemic arterial hypotension resulting from reflex vasodilatation, bradycardia, or both. Vasovagal syncope (VVS), mediated by emotional or orthostatic stress, is the most common cause of reflex syncope.

Non-pharmacological treatment, consisting of lifestyle advice and physical counterpressure manoeuvres (i.e. muscle tensing), is recommended as the first line of treatment for VVS in current syncope management guidelines. Patients are educated about the benign nature of the condition and are encouraged to increase the dietary salt and fluid intake (blood volume expansion) and to perform moderate exercise training. In a relatively mildly affected population the combination of lifestyle measures and physical counterpressure manoeuvres have been shown to decrease the syncope burden by 39%. However, it is yet unknown whether this combined non-pharmacological treatment is also effective in more severely affected patients.

Treatment of VVS should not only be directed at reducing the number of (pre-) syncopal recurrences, but should also aim to improve quality of life (QoL). QoL was found to be lower in patients with T-LOC compared to healthy subjects. Linzer et al. reported a level of impairment similar to severe rheumatoid arthritis and chronic low back pain. QoL in patients with T-LOC was found to be influenced by age, gender, co-morbidity, time of onset and frequency of syncopal recurrences as well as occurrence of pre-syncope. However, the effect of non-pharmacological treatment on QoL is still unknown.

Upon non-pharmacological treatment, we expect both a decrease in the frequency of syncopal recurrence and an improvement in quality of life. Whether both these effects occur in patients with VVS is still unknown. Therefore, we prospectively determined the effects of non-pharmacological treatment for VVS both with respect to syncopal recurrence and QoL.
Methods

This study was conducted by the Syncope Treatment and Assessment network Netherlands (STAND). Patient inclusion of this non-randomized study took place at the Emergency Departments and syncope units of 4 medical centres. All patients received non-pharmacological treatment, including lifestyle measures, and physical counterpressure manoeuvres. This combined treatment was evaluated both with respect to syncopal recurrences and QoL.

Study population

Patients between 18 and 70 years of age with a clinical diagnosis of recurrent VVS were eligible for inclusion. The diagnosis of VVS was based on the definition of the syncope management guideline of the European Society of Cardiology. We defined recurrent VVS as the occurrence of at least three syncopal episodes in the last 2 years.

Both patients with a certain clinical diagnosis based on history and physical examination and patients with highly likely VVS in combination with a positive head-up tilt-table test (HUT-test) were included. The induction of either pre-syncpe or syncope in the presence of hypotension (systolic blood pressure < 90 mm Hg) upon HUT-testing was defined as a positive response. Pre-syncpe refers to a condition in which patients feel as though syncope is imminent, but actual loss of consciousness does not occur. Only patients with recognizable prodromal symptoms in more than 80% of syncopal episodes of VVS were included.

Patients with orthostatic hypotension, suspected or confirmed heart disease with high likelihood of cardiac syncope, steal syndrome, episodes of loss of consciousness other than VVS, pregnancy and a life expectancy < 1 year were excluded. Patients with a high likelihood of study drop-out before the ending of the study as assessed by the research physician were also excluded.

The Medical Ethical Committee of the Academic Medical Center in Amsterdam approved the study (project number 03/191). The trial was registered in the Dutch Trial Register (ISRCTN29932893) and performed according to the declaration of Helsinki.
Non-pharmacological treatment

After obtaining written informed consent, study participants were given a handout with lifestyle advice. Patients were instructed to avoid - if possible - conditions in which prior episodes of (pre-)syncope occurred. An adequate fluid intake and high salt intake (accomplished by liberal addition of salt to meals) were advised; excessive alcohol intake was discouraged. All patients were also encouraged to physically exercise several times a week.9

During a biofeedback training session in physical counterpressure manoeuvres, the influence of leg-crossing, tensing of buttock and leg muscles, squatting, handgrip and arm tensing on finger arterial blood pressure was demonstrated. Details on how to perform these manoeuvres have been described elsewhere.2, 9 Finger arterial pressure was measured beat-to-beat by means of a Nexfin® (BMEYE B.V., Amsterdam, the Netherlands) or a similar device.14 Patients practiced the physical counterpressure manoeuvres with the continuous blood pressure tracing on a computer screen as feedback to gain optimal performance.

In this study, the combined effects of lifestyle measures, including assurance of an adequate fluid and salt intake, and physical counterpressure manoeuvres were determined.

Follow-up

We asked patients to register date and symptoms of subsequent recurrences under non-pharmacological treatment measures in a logbook. At 1, 3, 6, 9, 12, 15, and 18 months after inclusion, we obtained information about syncopal recurrence, usage of physical counterpressure manoeuvres and also their perceived effectiveness. Patients were contacted by telephone or seen at the outpatient-clinic.

Pharmacological treatment

The study protocol allowed patients to receive pharmacological treatment after 6 months of follow-up, if they had experienced three or more syncopal and/or severe pre-syncopal episodes during follow-up. Since we only evaluated the effects of non-pharmacological treatment in this present study, follow-up ended at the start of pharmacological treatment.

Quality of life

QoL was measured at four time points: before treatment initiation and after 3, 12, and 18 months of follow-up. If pharmacological treatment was started, QoL was also assessed just prior to this treatment.

Generic QoL was assessed using the short form-36 (SF-36) questionnaire. This self-administered questionnaire consisting of 36 items measures generic health
concepts relevant across age, disease, and treatment groups. After completing this questionnaire, eight scale scores can be calculated: physical functioning, role functioning physical, bodily pain, general health, vitality, social functioning, role functioning emotional, and mental health. The scores can be summarized into two scales, the physical and mental component summaries. All raw scale scores are converted linearly to a scale ranging from 0 to 100 (maximum). The higher the scores within this range, the higher the level of functioning or well-being. Translation, validation and norming of the Dutch-language version have been performed previously.

Disease-specific QoL was measured using the Syncope Functional Status Questionnaire (SFSQ). This questionnaire consists of 11 yes/no questions to assess syncope interference with a patient’s life and three 8-point Likert-scale questions assessing fear and worry with respect to syncope. The impairment score is calculated in two steps. Firstly, the number of areas in which syncope interfered with a patient’s life (range 0 to 11) is divided by the number of areas that were applicable to patients. Secondly, the obtained number is multiplied by 100, resulting in a score between 0 and 100, with 100 representing impairment in all areas that are applicable to patients. The three Likert-scale questions are averaged to calculate a fear/worry score scaled from 0 to 100, with 100 indicating maximum fear and worry. The Syncope Dysfunction Score (SDS) represents the averaged impairment score and fear/worry score. The higher this score, the worse syncope-related QoL. In a previous study, the validity, reliability and responsiveness of the Dutch version of the SFSQ have been determined.

Statistical analysis
We expressed demographic and clinical data as proportions for categorical data, means (SD) for normally distributed continuous data and median with quartiles for variables with non-normal distributions.

We expressed the frequency of syncopal recurrence in several ways. The syncope burden was calculated by dividing the total number of syncope episodes by the respective time period in years. We compared the syncope burden during the first year of treatment with the number of syncope during the last year before the start of treatment using a Wilcoxon signed rank test. The index episode of syncope was not included in the calculation of the syncope burden before treatment as this will increase this burden in comparison to the calculation of the syncope burden after treatment which is based on a fixed period, i.e. not necessarily ending with a syncopal episode.
A Kaplan-Meier curve was used to visualize the time to first recurrence of syncope. We used univariate Cox proportional hazards models to determine the effects of gender, age, syncope burden before treatment, and co-morbidity (represented by the Charlson comorbidity index\(^{17}\)) on syncopal recurrence. Predictors with a univariate p-value of 0.1 or lower were entered into a multivariable Cox proportional hazards model.

To analyze QoL at baseline and during follow-up, we used all available SF-36 and SFSQ questionnaires obtained at baseline and at 3, 12, and 18 months of follow-up. We calculated summary scores of the SF-36 and SFSQ questionnaires according to the guidelines of these respective questionnaires.\(^{19,20}\) For each of these questionnaires separately, we analysed all available summary scores using a linear mixed effects model including time as a categorical variable and the baseline value as a continuous covariate.\(^{18}\) Using this model, we tested the null hypothesis that the obtained scores at baseline were equal to the scores at 3, 12, and 18 months of follow-up. We expressed any change in QoL during the study period as difference in means with a 95% confidence interval (95% CI).

To evaluate associations between clinical changes and changes in QoL we calculated a patient’s relative improvement in syncope burden and QoL. The relative improvement in syncope burden was calculated based on the amount of syncopal recurrences in the year before the start of treatment excluding the last episode that led to the health care visit (A) and the syncope burden during the first year of treatment (B) using the following formula: \([ (A - B) / A ] \times 100\%\). If A and B were zero, we considered the relative improvement in syncope burden to be 0%. In case a patient had more episodes during treatment than before, the relative improvement could become larger than –100%, whereas in case of improvement the maximum improvement could not exceed 100%. This might lead to a distorted picture and therefore we also put a limit of –100% in case of worsening during treatment.

Changes in QoL were calculated in two steps. We first calculated patients’ mean summary scores of all available SFSQ and SF-36 questionnaires during 1 year of follow-up. Secondly, we calculated the difference between the mean summary score during 1 year of follow-up and the summary score at baseline in such a way that a positive difference indicated improved QoL during treatment. Using a scatter plot, we graphically displayed the relation between the relative improvement in syncope burden and the absolute improvement in QoL during the first year of follow-up. We determined the Spearman’s rank correlation between physical symptoms and QoL.

All data were analysed using SPSS 16.0 (SPSS, Chicago, IL, USA). If not specified otherwise, we considered a \(P < 0.05\) as statistically significant.
Results

Population
Between 2 January 2005 and the end of September 2008, 100 patients were included (Table 1). Mean age of the patients was 38 years and 34% were men. At inclusion, the median period since the first occurrence of syncope was 15 years [interquartile range (IQR) 6 - 26 years)]. The median number of syncopal episodes (without the index episode) in the year before study participation was three (IQR 1 - 6). Thirty-one percent of patients had experienced trauma due to VVS once or more in their lives, of which half were hematoma and/or wounds.

Follow-up was closed on 14 April 2009. Mean follow-up time was 12 months. No patients were lost to follow-up.

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>100</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>38 (14)</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>34%</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
</tr>
<tr>
<td>- Caucasian</td>
<td>88%</td>
</tr>
<tr>
<td>- Black</td>
<td>5.1%</td>
</tr>
<tr>
<td>- Asian</td>
<td>6.1%</td>
</tr>
<tr>
<td>- Hispanic</td>
<td>1.0%</td>
</tr>
<tr>
<td>Highest educational level (%)</td>
<td></td>
</tr>
<tr>
<td>- No formal education</td>
<td>1.0%</td>
</tr>
<tr>
<td>- Elementary school</td>
<td>5.2%</td>
</tr>
<tr>
<td>- High school</td>
<td>46%</td>
</tr>
<tr>
<td>- College</td>
<td>48%</td>
</tr>
<tr>
<td>Charlson comorbidity index (%)</td>
<td></td>
</tr>
<tr>
<td>- 0</td>
<td>86%</td>
</tr>
<tr>
<td>- 1</td>
<td>12%</td>
</tr>
<tr>
<td>- ≥ 2</td>
<td>2.0%</td>
</tr>
<tr>
<td>Period of complaints, years</td>
<td>Median (p25 – p75)</td>
</tr>
<tr>
<td>Number of syncopal episodes last 2 years</td>
<td>Median (p25 – p75)</td>
</tr>
<tr>
<td>Number of syncopal episodes last year</td>
<td>Median (p25 – p75)</td>
</tr>
<tr>
<td>Trauma due to (pre-)syncope (%)</td>
<td></td>
</tr>
<tr>
<td>- Hematoma/wound</td>
<td>15%</td>
</tr>
<tr>
<td>- Contusion/fracture</td>
<td>6.0%</td>
</tr>
<tr>
<td>- Head injury other than skin wounds</td>
<td>10%</td>
</tr>
</tbody>
</table>
Syncopal recurrence

Within the first 6 months of follow-up, 42% of patients had experienced syncopal recurrence(s). This percentage increased to 49% after one year. The syncope-free survival during follow-up is represented in Figure 1. The median syncope burden during the first year of non-pharmacological treatment was lower compared with the number of syncopal episodes in the year before treatment (0 vs. 3 respectively; \( P < 0.001 \); Table 2). The median time to syncopal recurrence after start of treatment was 59 days (IQR 15 - 125). Age as well as the syncope burden before study participation were associated with syncopal recurrence in the univariate Cox analysis. In multivariate analysis, effects were significant for patients with two or more syncopal recurrences per year before study participation (hazard ratio 2.8 (95% CI 1.1 – 7.1) for two to five prior syncopal recurrences (\( P = 0.03 \)); hazard ratio 3.9 (95% CI 1.6 – 9.6) for six or more prior syncopal recurrences (\( P = 0.004 \)).

Physical counterpressure manoeuvres were applied by 94% of patients within the first year (Table 2). Most (52%) of these patients reported that the manoeuvres were very beneficial to them. The most important reason for failure of physical counterpressure manoeuvres in case of syncopal recurrence was that syncope appeared too quickly to apply the manoeuvres (56% of cases). Twenty-five percent of patients reported that syncope still recurred though they managed to apply the physical counterpressure manoeuvres. Two patients (4%) were forgotten how to apply the manoeuvres to prevent syncopal recurrence.

Figure 1. Syncope-free survival.
Table 2. Number of syncopes and usage of physical counterpressure manoeuvres.

<table>
<thead>
<tr>
<th>Description</th>
<th>Median (p25 – p75)</th>
<th>All patients</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of syncopal episodes during the last year before treatment</td>
<td>3 (1 – 6)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Number of syncopes during the first year of treatment</td>
<td>1 (0 – 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days to first syncopal recurrence in case of syncopal recurrence</td>
<td>59 (15 – 125)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients that used physical counterpressure manoeuvres within first year of non-pharmacological treatment</td>
<td>94%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived benefit from physical counterpressure manoeuvres (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Very much</td>
<td>52%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Little</td>
<td>36%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Not at all</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main reason failure counterpressure manoeuvres in case of syncopal recurrence (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No/too short period of prodromal symptoms</td>
<td>56%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Forgot to use manoeuvres</td>
<td>4.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Manoeuvres performed, but ineffective</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Other reasons</td>
<td>15%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Quality of life
The Physical Component Summary scores obtained during follow-up were higher (i.e. improved QoL) than the summary score obtained at baseline (48 vs. 45; $P = 0.001$; Figure 2). The Mental Component Summary Scores at baseline and during follow-up were similar ($P = 0.28$). The estimated SDSs were lower during follow-up compared to baseline (34 vs. 22; $P < 0.001$), indicating an improvement in QoL.

Figure 2: Quality of life during non-pharmacological follow-up using a linear mixed effects model.

Improved quality of life is indicated by higher scores for the physical and mental component summary of the short form-36 questionnaire and lower scores with respect to the syncope dysfunction score of the syncope functional status questionnaire. The summary scores of both questionnaires can vary between 0 and 100.
Association between improvement in syncope burden and quality of life
The association between relative improvement in syncope burden and absolute improvement in QoL is displayed in Figure 3. In 63% of patients the syncope burden decreased during non-pharmacological treatment (total of quadrants B and D). Forty percent of patients showed both improvements in QoL and syncope burden. Only the correlation between absolute improvement in SDS and relative improvement in syncope-burden was statistically significant ($r = 0.32; P = 0.004$).

Figure 3: Relationship between improvement in quality of life and improvement in syncope burden during the first year of non-pharmacological treatment.
PCS-score: Physical Component Summary-score of the Short Form-36 (SF-36) questionnaire. MCS-score: Mental Component Summary-score of the SF-36 questionnaire. SDS-score: Syncope Dysfunction Score of the Syncope Functional Status Questionnaire (SFSQ). For both axes in the graphs, 0 was the threshold to discern improvement and deterioration. We separated each graph in four quadrants (A, B, C, and D) by drawing straight lines through the null-values of each axis and calculated the percentage of patients in each quadrant. A. Deterioration in syncope burden and improvement in quality of life. B. Improvement in both syncope burden and quality of life. C. Deterioration in both syncope burden and quality of life. D. Improvement in syncope burden and deterioration in quality of life. Note that syncopal recurrence decreased upon non-pharmacological treatment in 63% of patients (patients in quadrants B and D). In the majority of these patients (quadrant B), a decrease in syncopal recurrence upon treatment was associated with an improvement in quality of life.
Discussion

This is the first study in which the effectiveness of non-pharmacological treatment has been determined with respect to both changes in syncopal recurrences and QoL in VVS patients with frequent syncopal recurrences. In more than 60% of patients the occurrence of syncope episodes decreased during non-pharmacological treatment. However, nearly half of patients still experienced one or more syncopal recurrences within the first year of follow-up. QoL improved during non-pharmacological treatment and there was a slight positive association between larger reductions in syncope burden and more improvement in disease-specific QoL.

After diagnosing VVS, in addition to lifestyle measures patients are given instructions to perform physical counterpressure manoeuvres. These manoeuvres have been shown to be a risk-free and effective treatment method in patients with vasovagal syncope with prodromal symptoms. In the PC-trial, the proportion of patients with recurrence during on average 14 months of follow-up was lower in patients trained in physical counterpressure manoeuvres (32%) compared to patients that only received lifestyle advice (51%; \( P = 0.005 \)). Compared with this previous study, the proportion of patients with a recurrence during the combination of life style measures and manoeuvres was higher in our present study (49%, after a follow-up of 12 months). This higher percentage of recurrences can be explained by the selection of more severely affected patients in our study. We only included patients with three or more true syncopal episodes, whereas in the PC-trial also patients with three pre-syncopal episodes in the last year were included. Accordingly, the median number of syncopal episodes in the last 2 years before study participation was nearly twice as high in this present study compared to the PC-trial (5 vs. 3). Since the number of syncopal episodes before presentation is the main predictor of recurrence, the selection of patients explains the higher syncopal recurrence rate in this study.

We found that a syncope burden of two or more before study participation significantly increased the likelihood of syncopal recurrence. This confirms the earlier results by Sheldon et al. who found that both the number of previous syncopal episodes as well as the duration of syncopal symptoms were important to predict syncopal recurrences after diagnosis. In contrast with this previous study, the duration of symptoms was not a significant predictor of syncopal recurrence in our study.

It is well known that physical and psychosocial function are impaired in patients with T-LOC. In previous studies, QoL has been evaluated only once after treatment initiation, in combined groups of patients with various diagnoses and treatments.
In contrast, we prospectively evaluated QoL at consecutive time points during follow-up in a more homogeneous group of patients. We found that both the Physical Component Summary of the SF-36 questionnaire and the SDS significantly improved during treatment including physical counterpressure manoeuvres. Of these, only the change in Physical Component Summary seems to be of clinical significance, as only the improvement in this score was larger than the minimally important difference as found in an earlier study (3 vs. 0.7). The improvement in both the Mental Component Summary and SDS were smaller than the minimally important difference (1.2 vs 5.6 and 12 vs. 15, respectively). The clinical significance of these improvements is borderline, as the changes are just above (Physical Component Summary 3 vs. 0.7) or just below (Syncope Dysfunction Score 12 vs. 15) the minimal important difference as found in an earlier study. Nevertheless, mainly physical aspects of QoL seem to show a clinical significant change upon non-pharmacological treatment. In our view, a prolonged period of self-experienced treatment effectiveness is needed before patients feel confident about being able to prevent impending (pre-)syncopal recurrences. We expect that all domains of QoL will increase as soon as patients feel confident about being able to prevent impending recurrences of VVS.

In most earlier studies assessing the change in QoL after treatment initiation, only the number of syncopal episodes after start of treatment, and not the change in syncope-burden was taken into account. Because of the inverse relationship between the lifetime number of syncopal episodes and QoL, we hypothesized that if syncope recurs less often during treatment than before treatment, QoL will also improve. Therefore, in our view changes in the frequency of syncopal recurrence are as relevant as the presence or absence of recurrence alone to evaluate treatment effectiveness. In our study, the correlation between relative improvement in syncopal recurrence and improvement in QoL was significant with respect to syncope-related dysfunctioning (r = 0.32; P = 0.004), but not when assessing physical and mental functioning in general. These findings indicate that general QoL in patients with VVS is not only determined by syncopal recurrence. Other factors such as co-morbidity and psychiatric complaints are likely to be involved.

Limitations

Our study was not randomized. All included patients openly received non-pharmacological treatment for VVS. Though we had originally planned to determine the additional effect of physical counterpressure manoeuvres to lifestyle advice in a randomized fashion, results from the PC-trial revealed that treatment including physical counterpressure manoeuvres was clearly more effective. Because of ethical
reasons, we decided to determine the effects of combined non-pharmacological treatment only. Since we did not examine the contribution of the components of the non-pharmacological treatment, we are unable to conclude anything about the effects of these individual treatment measures. Except for counterpressure manoeuvres, there is only circumstantial evidence about the benefits of adequate water and salt intake and regular exercise to prevent recurrent VVS.\textsuperscript{10, 21, 22}

In our single treatment study, we compared syncope burden before and after treatment, which should be interpreted with care. Sheldon \textit{et al.}\textsuperscript{23} have shown that many VVS patients present themselves after a recent worsening of their syncope. Moreover, if patients present after a recent worsening of their symptoms, syncopal recurrence is likely to decrease afterwards irrespective of the treatment given. Therefore, our focus was not only a reduction of episodes, but also on the absolute value of the proportion of patients having a recurrence in this population. In addition, we evaluated which patient characteristics were associated with recurrence and whether larger reductions in syncope burden were associated with more improvement in QoL. All these questions can be adequately addressed within our single treatment study.

Both at presentation and during follow-up, patients were asked about their frequency of VVS. We suspect that patients’ memory of recurrent episodes during one to 3 months of follow-up is better than their remembrance of episodes during their whole lives, also because in the study patients had been given a diary to record episodes of VVS. If this is true, the number of episodes before presentation is probably underestimated and the real treatment effect is likely to be larger than reported in this study.

Patients were allowed to receive pharmacological treatment after six or more months of follow-up if they suffered from three or more episodes of syncope or severe pre-syncope after the start of non-pharmacological treatment. Patients with fewer recurrences were likely to have a better QoL\textsuperscript{3, 6, 7} and were followed for a longer period than more severely affected patients. If we would have excluded the highly affected, pharmacologically treated patients from the analysis after ending of their non-pharmacological study treatment, QoL determined at later moments of follow-up would be too optimistic. We therefore chose to use a linear mixed effects model, allowing estimations of QoL at times QoL was supposed to be evaluated but was however unavailable.\textsuperscript{18} Although we think that the use of a mixed effects model is best to deal with missing QoL data over time, estimations might still be too optimistic or pessimistic, and therefore need to be interpreted with caution.
Conclusion

In patients with frequent syncopal recurrences, the number of syncopal recurrences decreases after initiation of non-pharmacological treatment, while QoL improves over time. We therefore conclude that non-pharmacological treatment is also beneficial to patients that are more severely affected by VVS, but only half of patients does not experience any episode of syncope. Non-pharmacological treatment should be recommended to all patients diagnosed with VVS, but some patients may require additional treatment.
Reference List


