Neurally-mediated reflex syncope: diagnosis and treatment

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Chapter 3

Diagnosing vasovagal syncope based on quantitative history-taking: validation of the Calgary Syncope Symptom Score

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Abstract

Background: It can be difficult to distinguish vasovagal syncope, the most common cause of transient loss of consciousness (T-LOC), from other causes of syncope by history-taking. The Calgary Syncope Symptom Score (Calgary Score) is a tool developed for this purpose. We studied its performance in a series of patients presenting with T-LOC.

Methods: We calculated the Calgary Score for 380 patients presenting with T-LOC to a number of departments of our university hospital. Diagnoses of vasovagal syncope based on the Calgary Score were then compared with the final diagnoses, obtained after additional testing and 2 years of follow-up.

Results: The sensitivity of the Calgary Score was 87% (95% CI: 82 to 91%), at a specificity of 32% (95% CI: 24 to 40%). Most items of the Calgary Score were less discriminative in our study group than in the original population. Incorrectly labelling patients with syncope as vasovagal was most common in patients with psychogenic pseudosyncope (specificity 21%) but also occurred in patients with cardiac syncope (specificity 32%).

Conclusions: The sensitivity of the Calgary Score was comparable with the one in the original study, but its specificity was much lower, limiting its value in patients presenting with T-LOC in a general hospital setting.
Introduction

Transient loss of consciousness (T-LOC) is either due to syncope or non-syncope.\textsuperscript{1} Syncope is a self-limited episode of T-LOC due to a transient hypoperfusion of the brain.\textsuperscript{2} It can be caused by various conditions, ranging from benign ones such as reflex syncope to more severe and potentially lethal ones such as cardiac syncope.\textsuperscript{3} Epilepsy and psychogenic pseudo-syncope are examples of non-syncopal T-LOC.\textsuperscript{1} Since prognosis and treatment differ for the various forms of T-LOC,\textsuperscript{1,3} obtaining a correct diagnosis is essential for appropriate management of patients.

Clinical history-taking is the cornerstone of diagnosing patients presenting with T-LOC.\textsuperscript{4,5} However, distinguishing vasovagal syncope (VVS, the most frequent cause of reflex syncope)\textsuperscript{3,6} from other types of T-LOC by history taking can be difficult. The Calgary Syncope Symptom Score (hereafter abbreviated as Calgary Score) has been developed as a diagnostic tool to discern VVS from other types of syncope.\textsuperscript{7,8} The Calgary Score consists of 7 diagnostic questions. Each answer is associated with points, and a total score is calculated by summing the points. Patients with a total score on or above the threshold are classified as having VVS, patients below the threshold as not having VVS.

The Calgary Score was developed in a relatively small study population, with clear syncope diagnoses, and within the specific setting of patients presenting with syncope at Cardiology departments.\textsuperscript{8} Patients with diagnoses that were less clear were excluded from the analyses used to develop the diagnostic guideline. However, in clinical practice, patients with T-LOC are being evaluated at various hospital departments. Often the precise cause of T-LOC, either syncope or non-syncope, is unclear after initial evaluation. A decision rule to diagnose patients presenting with T-LOC can therefore only be useful, if application to all patients presenting at different clinical settings with either syncopal or non-syncopal causes of T-LOC is possible. In addition, reliable evidence about the diagnostic performance of the Calgary Score is crucial, since misclassification of patients as having VVS who in reality suffer from more severe causes of T-LOC can have serious, sometimes even lethal consequences.

Thus, though the Calgary Score is currently being used in clinical practice,\textsuperscript{7,9} it has never been validated in an external population. In this study, we have therefore determined the diagnostic performance of the Calgary Score in an independent series of patients presenting with T-LOC to various clinical departments.
Methods

Study design
The data for the present study were collected in a prospective cohort study designed to assess and compare the value of diagnostic strategies for adult patients presenting with T-LOC at a single university teaching hospital. That study is reported in detail elsewhere.10

Patients
Consecutive patients presenting with T-LOC to the Academic Medical Centre Amsterdam were eligible for inclusion.10 T-LOC was defined as a self-limiting episode of loss of consciousness not due to head trauma, lasting no longer than 1 h.10 Our study complies with the Declaration of Helsinki.11 The Medical Ethical Committee of our institution approved the research protocol. All included patients gave informed consent.

Inclusion and exclusion criteria
Patients presenting with an episode of T-LOC were included at the departments of Neurology, Cardiology, Internal Medicine, Emergency Department and Cardiac Emergency room.10 Patients could have experienced similar episodes previously, but those with a well-established earlier diagnosis for their T-LOC and patients younger than 18 years of age were excluded. As patients with epileptic seizures, cardiomyopathy and/or prior myocardial infarction were excluded from the analysis in the study in which the Calgary Score was developed,8 we also excluded these patients from our study. Patients without a final diagnosis after 2 years of follow-up were also excluded, since it is uncertain whether VVS was present or absent in these patients.

Calgary Score calculation
The Calgary Score consists of seven diagnostic questions about the medical history, triggers, circumstances and signs and symptoms of T-LOC (Table 1).8 All questions are answered as ‘yes’ or ‘no’. If a question is answered as ‘yes’, points are added or subtracted, depending on whether an answer increases the likelihood of VVS or not. The points for individual questions are then summed to obtain a total score (range: -14 to +6 points). If the total score is -2 or more positive, a Calgary Score diagnosis of VVS is made.8

The Calgary Score was originally developed in a cohort of 323 patients, of whom 235 had VVS confirmed by a positive tilt test and 88 had other forms of syncope.8 The seven diagnostic questions of the Calgary Score were selected from a potential
group of 118 historical items using a backward selection method. The additional discriminative value of each question conditional on responses to the other questions was determined in a multivariable logistic regression model, and question points were based on the magnitude of the corresponding coefficients. In the current study, the attending physicians took a standardized medical history, using a questionnaire similar to the guideline of the European Society of Cardiology. This study has been developed to determine the diagnostic yield of initial evaluation. The attending physicians did not know that the diagnostic accuracy of the Calgary Score would be calculated. The questionnaire used in this validation study contained questions about socio-demographic factors, a detailed T-LOC history and history of other medical conditions. This information enabled us to calculate a Calgary Score for each patient. We applied the same cut-off value to obtain a Calgary Score diagnosis of VVS.
Table 1. Individual items of the Calgary Score.8

<table>
<thead>
<tr>
<th>Question</th>
<th>Points (if yes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is there a history of at least one of bifascicular block, asystole,</td>
<td>–5</td>
</tr>
<tr>
<td>supraventricular tachycardia, diabetes?</td>
<td></td>
</tr>
<tr>
<td>2. At times have bystanders noted you to be blue during your faint?</td>
<td>–4</td>
</tr>
<tr>
<td>3. Did your syncope start when you were 35 years of age or older?</td>
<td>–3</td>
</tr>
<tr>
<td>4. Do you remember anything about being unconscious?</td>
<td>–2</td>
</tr>
<tr>
<td>5. Do you have lightheaded spells or faint with prolonged sitting or standing?</td>
<td>1</td>
</tr>
<tr>
<td>6. Do you sweat or feel warm before a faint?</td>
<td>2</td>
</tr>
<tr>
<td>7. Do you have lightheaded spells or faint with pain or in medical settings?</td>
<td>3</td>
</tr>
</tbody>
</table>

The patient has vasovagal syncope if the total point score is ≥ -2.

Patients with known cardiomyopathy and myocardial infarction are excluded from analysis.

**Final diagnosis: further testing and additional follow-up**

Based upon the structured questionnaire, the findings of a physical examination and a 12-lead ECG, the attending physician formulated a working diagnosis.10 In case other diagnoses were suspected, appropriate additional diagnostic tests were performed. If the diagnosis of T-LOC remained unknown after initial evaluation, cardiac evaluation (echocardiography, 24 h Holter monitoring, and exercise ECG) and, if this revealed no diagnosis, a tilt-table test and carotid sinus massage were performed. In all patients, treatment was initiated according to the ESC-guidelines.1 After at least 2 years of follow-up, a final diagnosis was assigned based on data from the initial presentation, results from additional testing, response to treatment, and additional diagnostic information during follow-up.10

A diagnosis of VVS was made if a trigger (such as fear, pain, and long standing) was associated with prodromal signs and symptoms (such as nausea, light-headedness, and diaphoresis),1 or if a less typical history was confirmed by a positive tilt-table test and/or information from follow-up, and no other cause of T-LOC was found after additional testing and follow-up.10 Vasovagal syncope was considered not to be present in case another diagnosis of T-LOC was made.10

Psychogenic pseudosyncope is used for patients who seem unconscious with no physiologic cause present.1,12 In our study, a final diagnosis of psychogenic pseudosyncope was made if the clinical history of the patient presenting with T-LOC was very atypical [e.g. prolonged unexplained unconsciousness in supine position (10-30 min), highly frequent episodes (up to several times a day), tight eye closure
during the episodes], and/or T-LOC occurred during tilt-table testing or clinical observation without a drop in blood pressure and/or heart rate in patients without another cause of T-LOC. A final diagnosis of psychogenic pseudosyncope was only made after consultation with a psychiatrist specialized in functional disorders. The diagnostic criteria that were used for other causes of T-LOC have been published before. In the cases where the initial diagnosis was rejected or changed, the patient had died during follow-up or there was any doubt on the final diagnosis, an expert committee, consisting of an expert neurologist, cardiologist and internist reviewed all these cases at the end of at least 2 years of follow-up. The expert committee reviewed all available information summarized per patient and made a final diagnosis for each patient. At all times, patients, physicians and expert panel were unaware that a validation study would be performed.

The final diagnoses of patients obtained after additional testing, 2-years of follow-up and, if necessary, expert committee review were used as a reference standard in this study.

Statistical analysis
Continuous variables were summarized as means and standard deviations, or medians and quartiles (p25-p75) if the distribution was not normal. Differences in means between groups were tested with two-sided t-test statistics, or the Mann-Whitney test statistic. We summarized dichotomous variables as proportions with 95% confidence intervals (Cis) calculated using the Wilson method and used Chi-square tests to compare them between groups.

Diagnostic accuracy
We determined the diagnostic accuracy of the Calgary Score by comparing diagnoses based on the score with the final diagnoses. We calculated the sensitivity, specificity, and positive and negative predictive values of the Calgary Score diagnosis of VVS. Since the relative frequency of causes and signs and symptoms of T-LOC differ between older and younger patients, we separately determined the diagnostic accuracy in patients under 50 years of age and in patients aged 50 years or above. We evaluated the specificity in a number of subgroups of patients with a final diagnosis other than VVS. We also summarized the Calgary Score distributions for patients with and without a final diagnosis of VVS in a graph.

Diagnostic value of each item of the Calgary Score
We counted the frequency of positive responses to each item of the Calgary Score among patients with and without final diagnosis of VVS and compared these to the
Validation of the Calgary Score frequencies reported in the development study, to evaluate whether specific items were more or less discriminative in this validation study.

All data were analysed using SPSS 16.0 (SPSS, Chicago, IL, USA). P-values <0.05 were considered statistically significant.

Results

Study group
A total of 503 patients were included between February 2000 and May 2002 (Figure 1). Fifty-five patients with a history of cardiomyopathy or myocardial infarction and 18 patients with epileptic seizures were excluded, to match the exclusion criteria of the original publication. Also, 50 patients with an unknown cause of T-LOC were excluded. Our validation cohort, therefore, consisted of 380 patients presenting with T-LOC.

In total, 237 patients (55%) were diagnosed with VVS after additional testing and 2 years of follow-up, while 143 patients suffered from other causes of T-LOC (Figure 1). The most frequent diagnoses in the latter group were: neurally-mediated reflex syncope other than VVS (n = 43), orthostatic hypotension (n = 44), and cardiac syncope (n = 28). Compared with patients with other causes of T-LOC, patients with VVS were younger (Table 2; P < 0.001). Gender and frequency of syncopal episodes did not differ between patients with VVS and patients with other diagnoses (P = 0.08 and P = 0.81, respectively).
Figure 1. Validation cohort: patient selection and final diagnoses after 2 years of follow-up.

Patients presenting with T-LOC  
\( n = 503 \)

- History of cardiomyopathy or myocardial infarction  
  \( n = 55 \)
- History of epileptic seizures  
  \( n = 18 \)
- Unknown cause of T-LOC  
  \( n = 50 \)

Patients included in analysis  
\( n = 380 \)

- Vasovagal syncope  
  \( n = 237 \)
- Other forms of T-LOC  
  \( N = 143 \)
  - Neurally-mediated reflex syncope, not vasovagal syncope  
    \( n = 43 \)
  - Orthostatic hypotension  
    \( n = 44 \)
  - Cardiac syncope  
    \( n = 28 \)
  - Psychogenic pseudosyncope  
    \( n = 24 \)
  - Neurological disorder  
    \( n = 3 \)
  - Metabolic disorder  
    \( n = 1 \)

T-LOC, transient loss of consciousness
Table 2. Characteristics of patients with and without a final diagnosis of VVS in the validation cohort.\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Final diagnosis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VVS</td>
<td>Other T-LOC-diagnoses</td>
</tr>
<tr>
<td>Total (n)\textsuperscript{a}</td>
<td>237</td>
<td>143</td>
</tr>
<tr>
<td>Mean follow-up time (years, SD)</td>
<td>2.6 (0.7)</td>
<td>2.5 (0.7)</td>
</tr>
<tr>
<td>Gender (n, %)</td>
<td>Male</td>
<td>114 (48%)</td>
</tr>
<tr>
<td>Age (n, %)</td>
<td>&lt;50 years</td>
<td>146 (61.6%)</td>
</tr>
<tr>
<td></td>
<td>50 years or above</td>
<td>91 (38.4%)</td>
</tr>
<tr>
<td>Frequency of syncope in last year (n, %)</td>
<td>≤1</td>
<td>93 (39.2%)</td>
</tr>
<tr>
<td></td>
<td>2–3</td>
<td>60 (25.3%)</td>
</tr>
<tr>
<td></td>
<td>≥4</td>
<td>84 (35.4%)</td>
</tr>
<tr>
<td>Frequency of pre-syncope per month (n, %)</td>
<td>&lt;1</td>
<td>69 (29.1%)</td>
</tr>
<tr>
<td></td>
<td>1–3</td>
<td>48 (20.3%)</td>
</tr>
<tr>
<td></td>
<td>≥4</td>
<td>120 (50.6%)</td>
</tr>
<tr>
<td>Duration T-LOC &lt; 1 minute (n, %)</td>
<td>77 (32.5%)</td>
<td>66 (46.2%)</td>
</tr>
</tbody>
</table>

VVS, vasovagal syncope. T-LOC, transient loss of consciousness.
\textsuperscript{a}After exclusion of patients with known cardiomyopathy, myocardial infarction, epileptic seizures and no diagnosis.

Diagnostic accuracy of the Calgary Score

A diagnosis of VVS based upon the Calgary Score was made in 380 patients within the validation cohort (Tables 3 - 5). The overall sensitivity of the Calgary Score diagnosis of VVS in our validation cohort was 87\% (95\% CI: 82 - 91\%). The sensitivity was 92\% (95\% CI: 86 - 95\%) for patients under 50 years of age, and 79\% (95\% CI: 70 - 86\%) for patients aged 50 years or above. The overall specificity of the Calgary Score diagnosis of VVS was 32\% (95\% CI: 24 - 40\%). The specificity was 22\% (95\% CI: 13 - 36\%) for patients under 50 years of age and 38\% (95\% CI: 27 - 46\%) for patients aged 50 years or above. In comparison with the original publication, the overall sensitivity was similar (87\% vs. 89\%), but the overall specificity in the validation cohort was much lower (32\% vs. 91\%).

In Figure 2, the total point scores of individual patients with and without a final diagnosis of VVS are shown. Although the distribution between the two groups is significantly different, there is a large overlap in total scores between the two groups.
Table 3. Diagnostic accuracy of the Calgary Score in the validation cohort.

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>VVS present</th>
<th>VVS absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calgary Score diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VVS present</td>
<td>206</td>
<td>98</td>
<td>304</td>
</tr>
<tr>
<td>VVS absent</td>
<td>31</td>
<td>45</td>
<td>76</td>
</tr>
<tr>
<td>Total</td>
<td>237</td>
<td>143</td>
<td>380</td>
</tr>
</tbody>
</table>

Sensitivity = 206/237 = 87% (95% CI 82-91%) (Original publication: 89%)
Specificity = 45/143 = 32% (95% CI 24-40%) (Original publication: 91%)
Positive predictive value = 68% (95% CI 62-73%) (Original publication: 96%)
Negative predictive value = 59% (95% CI 48-70%) (Original publication: 75%)

Table 4. Diagnostic accuracy of the Calgary Score in the validation cohort for patients under 50 years of age.

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>VVS present</th>
<th>VVS absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calgary Score diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VVS present</td>
<td>134</td>
<td>35</td>
<td>169</td>
</tr>
<tr>
<td>VVS absent</td>
<td>12</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>146</td>
<td>45</td>
<td>191</td>
</tr>
</tbody>
</table>

Sensitivity = 134/146 = 92% (95% CI 86-95%)
Specificity = 10/45 = 22% (95% CI 13-36%)
Positive predictive value = 79% (95% CI 73-85%)
Negative predictive value = 46% (95% CI 27-65%)

Table 5. Diagnostic accuracy of the Calgary Score in the validation cohort for patients aged 50 years or above.

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>VVS present</th>
<th>VVS absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calgary Score diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VVS present</td>
<td>72</td>
<td>63</td>
<td>135</td>
</tr>
<tr>
<td>VVS absent</td>
<td>19</td>
<td>35</td>
<td>54</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>98</td>
<td>189</td>
</tr>
</tbody>
</table>

Sensitivity = 72/91 = 79% (95% CI 70-86%)
Specificity = 35/98 = 38% (95% CI 27-46%)
Positive predictive value = 53% (95% CI 45-62%)
Negative predictive value = 65% (95% CI 52-76%)
Figure 2. Distribution of total diagnostic point scores of the Calgary Score among patients with and without a final diagnosis of vasovagal syncope (VVS).

**Diagnostic value of individual items of the Calgary Score**

We compared the discriminative value of each individual diagnostic question in the validation cohort with the corresponding value in the development cohort. Table 6 shows that the discriminative value of most diagnostic questions was lower in the validation cohort compared with the development cohort.

**Performance of Calgary Score in specific subgroups of patients**

We examined whether specific types of other diagnoses than VVS were responsible for the low specificity of the Calgary Score in our validation cohort by calculating subgroup-specific specificities (Table 7). The specificities of these diagnoses were not significantly different from each other ($P = 0.61$). The specificity in the subgroup of patients with a cardiac cause for their syncope was 32%. In other words, 68% of these patients ($n = 19$) would have been incorrectly diagnosed as having VVS by the Calgary Score. In the majority of these patients, diagnostic questions 3 and 5 of the Calgary Score (Table 1) were positive ($n = 16$ and $n = 18$, respectively). Patients with psychogenic pseudosyncope had a remarkable low subgroup-specific specificity of 21% (Table 7).
Table 6. Frequency of positive responses to individual diagnostic questions of the Calgary Score in patients with and without vasovagal syncope in the validation cohort (FAST-study) compared to the development cohort (Calgary Syncope Symptom Study).

<table>
<thead>
<tr>
<th>Diagnostic questions Calgary Score</th>
<th>Validation cohort</th>
<th>Development Cohort</th>
<th>Odds ratio</th>
<th>ROR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VVS n = 237</td>
<td>VVS n = 235</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other T-LOC</td>
<td>Other T-LOC</td>
<td>odds ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>diagnoses n = 143</td>
<td>diagnoses n = 88</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Is there a history of at least one of bifascicular block, asystole, supraventricular tachycardia, diabetes?</td>
<td>13%</td>
<td>23%</td>
<td>0.50</td>
<td>3.4%</td>
<td>64%</td>
</tr>
<tr>
<td>2. At times have bystanders noted you to be blue during your faint?</td>
<td>2.1%</td>
<td>4.9%</td>
<td>0.42</td>
<td>1.3%</td>
<td>8.0%</td>
</tr>
<tr>
<td>3. Did your syncope start when you were 35 years of age or older?</td>
<td>42%</td>
<td>78%</td>
<td>0.20</td>
<td>28%</td>
<td>91%</td>
</tr>
<tr>
<td>4. Do you remember anything about being unconscious?</td>
<td>0%</td>
<td>0%</td>
<td>0</td>
<td>31%</td>
<td>53%</td>
</tr>
<tr>
<td>5. Do you have lightheaded spells or faint with prolonged sitting or standing?</td>
<td>85%</td>
<td>83%</td>
<td>1.22</td>
<td>69%</td>
<td>38%</td>
</tr>
<tr>
<td>6. Do you sweat or feel warm before a faint?</td>
<td>65%</td>
<td>43%</td>
<td>2.49</td>
<td>62%</td>
<td>24%</td>
</tr>
<tr>
<td>7. Do you have lightheaded spells or faint with pain or in medical settings?</td>
<td>32%</td>
<td>15%</td>
<td>2.74</td>
<td>48%</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

ROR, relative odds ratio indicating how much more or less discriminative a diagnostic question is in the development cohort compared with the validation cohort by examining the ratio of both odds ratios.

*The answer to this diagnostic question was ‘no’ in all patients.
Table 7. Performance of Calgary Score in subgroups of patients with a final diagnosis other than vasovagal syncope in the validation cohort.

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>Calgary Score diagnosis not VVS</th>
<th>Calgary Score diagnosis VVS</th>
<th>Specificity diagnosis other than VVS (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurally mediated reflex syncope</td>
<td>14</td>
<td>29</td>
<td>33% (95% CI 21-48%)</td>
<td>0.61</td>
</tr>
<tr>
<td>(not vasovagal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>15</td>
<td>29</td>
<td>34% (95% CI 22-49%)</td>
<td></td>
</tr>
<tr>
<td>Cardiac syncope</td>
<td>9</td>
<td>19</td>
<td>32% (95% CI 18-51%)</td>
<td></td>
</tr>
<tr>
<td>Neurological disorder</td>
<td>2</td>
<td>1</td>
<td>67% (95% CI 21-94%)</td>
<td></td>
</tr>
<tr>
<td>Psychogenic pseudosyncope</td>
<td>5</td>
<td>19</td>
<td>21% (95% CI 9-41%)</td>
<td></td>
</tr>
<tr>
<td>Metabolic syncope</td>
<td>0</td>
<td>1</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

* Not calculated because of small number.

Overall specificity Calgary Score: 32%

Discussion

This is the first study evaluating the Calgary Score in a series of patients presenting with T-LOC to various departments in a large hospital. Although the sensitivity was similar in our study compared with the original publication, the specificity of the Calgary Score was much lower, implying that a large number of patients would receive an incorrect diagnosis of VVS based on the Calgary Score, while in reality they had a different cause for their T-LOC.

The methods of patient selection differed considerably between our validation study and the original study. The original study of Sheldon et al. only included patients with a typical manifestation (clear but strict rules) of the condition of interest (VVS) which is then contrasted with a well-defined group of patients with a different diagnosis for their T-LOC (controls). By including only well-defined cases and controls, the difference between these two groups is increased, making it easier for a test to distinguish cases and controls. There is both theoretical and empirical evidence that such an approach can lead to (severely) overoptimistic estimates of diagnostic accuracy. Therefore, we used a different approach in our validation study by including a group of consecutive patients presenting with T-LOC.
Unfortunately, there is no gold standard test to diagnose patients presenting with T-LOC. This implies that the final classification in any diagnostic study about T-LOC is challenging and the problem of misclassification always exists. In our study, a patient’s final diagnosis was based on three different sources of information: (i) standardized and prospectively collected information of history and physical examination; (ii) results of additional tests performed as recommended by the ESC Guidelines on syncope; (iii) dedicated follow-up information of at least 2 years of all patients including any additional testing, specific events, or causes of death. Such an approach is clinically appealing, because all these factors can provide important information, but a single factor is often not conclusive. To combine these multiple pieces of information, a team of experts reviewed and interpreted information obtained during initial evaluation and clinical follow-up and made a consensus diagnosis. The expert panel approach has been advocated in the literature for situations where a (single) gold standard does not exist.

Other factors that could explain the observed difference in diagnostic accuracy between the original study and validation study include differences in setting and methodology. In the original study, patients were only recruited from cardiology departments and syncope units, whereas in our study patients were recruited from several different departments. This difference could explain the relatively high frequency of cardiac causes and relatively low frequency of non-cardiac causes in the original study. For example, orthostatic hypotension was found to be present in only one patient in the original study compared with 44 patients in our study. Additionally, more advanced or more typical cardiac causes seemed to be present in the original publication.

The difference in setting also helps to explain why patients in our population were older than the patients in the original cohort. It is known that patients aged 65 years or above experience less prodromal signs and symptoms. Because of this, it becomes more difficult with advancing age to differentiate between different causes of T-LOC based on historical criteria alone. Additionally, in older patients, the cause of their episodes is more often multifactorial, and therefore less likely to fit one diagnostic group. The sensitivity of the Calgary Score was therefore lower for patients aged 50 years or above (79%) compared with younger patients (92%).

A methodological issue that deserves attention is the way the Calgary Score has been developed. The Calgary Score was developed using a data-driven approach, based on multiple variables and a backward elimination strategy. An important drawback of such an approach is that variables can be included in the final model
due to associations based on chance in a particular dataset rather than a true, robust relationship. This is known as overfitting. Overfitting is more likely, if the number of potential variables considered for inclusion is large in relation to the sample size. The authors in the original publication considered 118 potential variables for inclusion on a total of 235 patients with a final diagnosis of VVS. If overfitting is present, the performance of the model is likely to drop considerably when applied in a new series of independent patients. Although the authors used bootstrapping to correct for the likely overoptimism in their model, it has been shown that this method may be insufficient and may not be indicative for the model’s performance in future patients.

Probably due to the data-driven approach, the selection and the weights of two of the seven diagnostic questions in the Calgary Score are questionable. Diagnostic question 4, whether patients remember anything about being unconscious (Table 1), is probably used to determine whether the patient has truly lost consciousness, since remembering anything at the moment of true loss of consciousness seems impossible. In our validation cohort, the answer to this question was ‘no’ in all patients. In contrast, 47% of patients in the original study reported to remember anything about being unconscious. This difference in reporting can almost certainly be explained by differences in data collection. In the study in which the Calgary Score was developed, data were derived from self-administered questionnaires, while in our validation study an attending physician took the history of patients. Interviewer-administered questionnaires have been shown to be more reliable than self-administered questionnaires for medical histories.

The other peculiarity is the large number of points that is assigned if diabetes mellitus is present in a patient (-5 points for question 1), irrespective of the presence of cardiac rhythm disturbances. If diabetes mellitus is present in a patient, it becomes more difficult to obtain a Calgary Score diagnosis of VVS (total point score ≥ -2). Though instability of cerebral blood flow due to autonomic failure can occur in patients with diabetes, there is no evidence that the diagnosis of VVS is more unlikely in these patients than in patients without diabetes. Accordingly, we found that 9 of the 31 patients with a false-negative diagnosis of VVS had diabetes mellitus.

**Strengths and limitations**

Several characteristics of our study deserve attention when interpreting the results. An issue already addressed is the validity of the final diagnosis. We used all available data of history taking, physical examination and additional testing and dedicated follow-up of at least 2 years in all patients. Follow-up is useful because subsequent
events or additional testing may reveal relevant information on the accuracy of the diagnosis. However, even after 2 years of follow-up, the diagnosis was still unclear in 50 patients. This is a problematic group when evaluating the accuracy of this diagnostic tool, because it is unknown whether VVS has occurred. We excluded this group when calculating the accuracy of the Calgary Score (specificity of 32%); the specificity of the Calgary Score would drop to 30% if these patents would be included in the non-VVS group.

Another problem is that patients over time may experience T-LOC episodes with different causes. To reduce this problem, we only included patients without a previously diagnosed cause of T-LOC.

**Role of quantitative history-taking**

In this study, we found a high number of patients who would have received a diagnosis of vasovagal syncope according to the Calgary Score but in reality had another cause for their T-LOC (specificity of 32%). The requirements for a test (e.g. minimum sensitivity and specificity) vary depending on the clinical consequences associated with false-positive or false-negative test results and the intended role of the test in clinical practice. The mortality rate and morbidity in patients with a cardiac syncope or T-LOC due to neurological disorders is much higher than in patients with VVS. This implies that diagnosing patients actually suffering from a non-vasovagal cause of T-LOC as suffering from VVS (false-positives in this study) is worse than classifying patients with VVS as suffering from cardiac syncope (false negatives).

Because of its low specificity, we do not recommend to use the Calgary Score as a sole measure to diagnose individual patients presenting with T-LOC in clinical practice. Because there is no gold standard, we think the best way to obtain a diagnosis still consists of an integration of diagnostic information from medical history, physical examination, and additional testing, as recommended by the ESC Guideline on syncope. However, it sometimes remains quite difficult to integrate and weigh these multiple pieces of information, especially if there is a significant variation in presentation between patients, as occurs in patients with reflex syncope in general and VVS more specifically. Therefore, new, externally validated diagnostic rules could be very useful to discern malignant and benign causes of T-LOC. More targeted diagnostic rules might be necessary to discriminate between particular diagnoses, taking into account variations in presentations between patients.
Reference List