Angina, as a manifestation of ischemic heart disease, is a highly relevant clinical condition that affects ≈20% of patients 1 year after a myocardial infarction,1 ≈25% to 30% of patients 1 year after bypass graft surgery or multi-vessel stenting,2 and ≈45% of patients with stable ischemic heart disease.3 Beyond the direct morbidity of the symptoms experienced by the patient, angina is associated with worse health-related quality of life and is a major driver of repeat hospitalizations and increased healthcare costs.4 As a result, there have been numerous trials of different therapies to reduce angina,5–12 with the aim of simultaneously reducing its associated morbidity and costs. In designing such trials, the accurate quantification of the frequency and severity of angina among patients with ischemic heart disease is critical for comparing treatment efficacy. Moreover, health status (symptoms, function, and quality of life) has been endorsed as an outcome-based performance measure to assess healthcare quality in patients with ischemic heart disease.13 The gold standard for measuring angina frequency in clinical trials is considered to be either daily angina diaries or time to ischemic ECG changes or symptoms on an exercise treadmill test.5–12 However, these approaches are expensive, time consuming, generally not feasible for long-term assessment of treatments, and cannot be practically implemented in clinical care or quality assessment efforts.

The Seattle Angina Questionnaire (SAQ) is a self-administered, disease-specific health status questionnaire that measures clinically important dimensions of health in patients with ischemic heart disease. The SAQ angina frequency domain was significantly correlated, both cross sectionally and longitudinally, with daily diary entries of angina frequency and SL NTG use. These data further support the validity of the SAQ angina frequency domain across a broad spectrum of patients with stable angina.

**Conclusion**

In a multinational cohort of patients with stable angina, the SAQ angina frequency domain was significantly correlated, both cross sectionally and longitudinally, with daily diary entries of angina frequency and SL NTG use. These data further support the validity of the SAQ angina frequency domain across a broad spectrum of patients with stable angina.

**Clinical Trial Registration**


(Circ Cardiovasc Qual Outcomes. 2014;7:00-00.)

**Key Words:** health status ■ chronic stable angina ■ coronary artery disease
WHAT IS KNOWN

- The Seattle Angina Questionnaire is widely used to measure disease-specific health status among patients with coronary artery disease, but it has not been validated against daily records of angina frequency and sublingual nitroglycerin, the putative gold standard for measuring angina over time.

WHAT THE STUDY ADDS

- Using data from 917 patients with stable angina from the multinational Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina (TERISA) trial, we found that the Seattle Angina Questionnaire angina frequency scale was significantly correlated with daily diary entries on angina and sublingual nitroglycerin both cross sectionally and longitudinally (ie, comparing change in one measure versus change in the other)—correlations that were generally consistent by age, sex, and geographic region.
- Furthermore, we found that the Seattle Angina Questionnaire was most strongly correlated with diary entry using a 4-week recall, compared with shorter time periods, which provides empirical support that a 4-week recall period is reasonable for the patient-reported outcome of angina.
- These data support the validity of the Seattle Angina Questionnaire angina frequency domain, which is more practical to administer than a daily diary, and its continued use as a clinically relevant outcome for clinical trials of therapies that are designed to reduce angina and improve quality of life, as well as its use in clinical care and quality assessment.

Outcome Assessment

Subjects were given a novel electronic diary (LogPad LV diary, PHT Corporation, Boston, MA) with built-in electronic prompts for daily entry. During both the placebo run-in period and the active treatment period, subjects were instructed to record and transmit the data to the coordinating center every evening, including the number of angina episodes and number of SL NTG doses taken in the past 24 hours.

Disease-specific health status was assessed with the SAQ at randomization (ie, after the run-in period; day 1) and at 8 weeks after study drug initiation or at study termination (in the case of patient withdrawal from the study). The SAQ is a 19-item questionnaire that measures 5 clinically important dimensions of health in patients with coronary artery disease: angina frequency, angina stability, physical limitations, treatment satisfaction, and disease-specific quality of life.

Methods

Study Overview

The study design and population, treatment protocol, follow-up procedures, and study end points of TERISA have been described previously. TERISA was a randomized, double-blind, placebo-controlled trial in which subjects with stable angina and type 2 diabetes mellitus (T2DM) were randomized to a 1000 mg twice daily dose of ranolazine or matched placebo for 8 weeks. Subjects were required to have both a documented history of T2DM and coronary artery disease and also required at least a 3-month history of chronic stable angina. Furthermore, subjects had to be treated with 1 or 2 antianginal therapies (β-blockers, calcium channel blockers, long-acting nitrates) at a stable dose for ≥2 weeks before study entry. Key exclusion criteria were New York Heart Association class III to IV heart failure symptoms, acute coronary syndrome in the 6 months before screening, planned coronary revascularization during the study period, and prior treatment with ranolazine.

Eligible subjects entered a 4-week, single-blind placebo run-in period to ensure compliance with diary entry and study medication (weeks −6 to day 1; Figure 1). Subjects taking >2 antianginal medications at screening were allowed to washout any additional antianginal therapies 2 weeks before the run-in period (weeks −6 to −4). After the run-in period, subjects were randomized to ranolazine (Gilead Sciences, Foster City, CA) or matching placebo for 8 weeks (day 1 to week 8). By protocol, concomitant antianginal medications were kept stable during the study. The study was conducted in 104 sites in 14 countries across Asia, Europe, and North America and was approved by the national regulatory authority in each participating country and by the institutional review board or local ethics committee for each site. All participating subjects provided written informed consent.

Figure 1. Timeline of outcomes assessment in Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina (TERISA) study. SAQ indicates Seattle Angina Questionnaire; and SL NTG, sublingual nitroglycerin.
Patient Population

Of the 949 randomized subjects in TERISA, 917 (97%) had complete diary and SAQ data and were included in our analyses. There were no significant differences in patient characteristics between those who were included and excluded from the analysis. Participants’ demographic and clinical characteristics are shown in Table 1. Overall, the mean age of the patients was 64±9 years, 61% were male, and 74% had experienced a prior myocardial infarction. Most of the patients were enrolled from Russia, Ukraine, or Belarus, with 29% of subjects enrolled from other counties. The mean daily compliance with diary entry was 96%.

Cross-Sectional Comparison

Over the final 4 weeks of the study (week 5–8), subjects reported having an average of 4.7±4.6 episodes of angina (range=0.0–38.4) per week and reported using an average of 3.1±4.9 SL NTG (range=0.0–50.0) per week. At the time of randomization (day 1), the mean SAQ AF score was 59.8±20.9. The distributions of diary responses for the frequency of angina and SL NTG use over the final 4 weeks of the study for the different categories of response to the corresponding SAQ AF questions are shown in Table 2 and Figure 2 (agreement of SAQ AF responses with mean diary responses is shown in Table 1).

Table 1. Baseline Characteristics of the Patients (n=917)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.7±5.5</td>
</tr>
<tr>
<td>Male</td>
<td>61.3%</td>
</tr>
<tr>
<td>White race</td>
<td>99.0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>95.4%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>79.8%</td>
</tr>
<tr>
<td>Current smoking</td>
<td>16.1%</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>73.9%</td>
</tr>
<tr>
<td>Prior angioplasty</td>
<td>40.4%</td>
</tr>
<tr>
<td>Prior bypass graft surgery</td>
<td>18.3%</td>
</tr>
<tr>
<td>Duration of diabetes mellitus, y</td>
<td>7.4±6.8</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>7.3±1.5</td>
</tr>
<tr>
<td>Taking antiplatelet medication</td>
<td>92.9%</td>
</tr>
<tr>
<td>Taking insulin</td>
<td>19.1%</td>
</tr>
<tr>
<td>Antianginal medications</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>90.3%</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>28.6%</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>33.4%</td>
</tr>
<tr>
<td>Statins</td>
<td>82.2%</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>88.0%</td>
</tr>
<tr>
<td>ACE-I/ARBs</td>
<td>87.9%</td>
</tr>
<tr>
<td>Randomized to ranolazine</td>
<td>49.7%</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
</tr>
<tr>
<td>Russia/Ukraine/Belarus</td>
<td>71.3%</td>
</tr>
<tr>
<td>Other countries</td>
<td>28.7%</td>
</tr>
<tr>
<td>Diary compliance (% of d)</td>
<td>95.9±4.9</td>
</tr>
</tbody>
</table>

ACE-I indicates angiotensin converting enzyme-inhibitor; and ARB, angiotensin II receptor blocker.
Compared with the theoretical range of daily diary responses expected to correlate with the Likert item responses of the SAQ (eg, reporting, on average, angina 1–3 times/week would be expected to correlate with a monthly report of 7–21 episodes of angina/week on the daily diary), the means and medians were close to the anticipated ranges. Overall, the SAQ AF responses corresponded to the diary responses, with correlation coefficients ($r$ values) of $-0.64$ for angina frequency (95% CI, $-0.67$ to $-0.60$) and $-0.69$ for SL NTG use (95% CI, $-0.73$ to $-0.66$; Table 3). However, at both extreme ends of angina, there was less agreement. For example, among patients reporting no angina on the SAQ, a few episodes of angina were reported on the daily diaries. Specifically, patients who reported no angina (or no SL NTG taken) on the SAQ over the prior 4 weeks reported an average of 1.3 angina episodes per week (or 0.9 SL NTG taken per week), although the median responses were closer to those anticipated (1.0 episode of angina per week and 0.0 doses of SL NTG taken per week). In addition, patients who reported ≥4 angina episodes (or SL NTG taken) per day on the SAQ reported an average of 20.7 episodes of angina per week (or 26.6 SL NTG taken per week), which is somewhat less than the diary numbers anticipated.

The correlations between the SAQ AF responses and the corresponding diary entry were similar by age, sex, and geographic region (Table 3). Finally, the overall SAQ AF domain score was also significantly correlated with diary responses, with correlation coefficients of $-0.61$ for angina frequency and $-0.64$ for SL NTG use ($P<0.0001$ for both). The correlations of the SAQ AF responses with the corresponding diary entry over different recall periods are shown in Table II in the Data Supplement. Both when angina was relatively stable (during placebo run-in period) and when angina was less stable (during antianginal treatment), the correlations between the SAQ AF responses and diary entries were strongest using the 4-week recall period and decreased slightly as the recall period shortened with the weakest correlation being observed with average daily angina diaries over the prior week.

### Longitudinal Comparison

Between randomization and study end (day 1 to week 8), SAQ AF scores increased by an average of 13.5±18.5 points. In the diaries, subjects reported an average of 2.2±3.7 fewer episodes of angina per week over the corresponding time. In addition, they reported using an average of 1.3±3.7 fewer SL NTG per week. The mean change in diary responses of the patients categorized by their change in SAQ AF scores is shown in Figure 3. Changes in SAQ AF scores were significantly associated with changes in diary responses, with correlation coefficients of $-0.42$ for angina frequency (95% CI, $-0.48$ to $-0.37$) and $-0.38$ for SL NTG use (95% CI, $-0.43$ to $-0.33$).

### Table 2. Distribution of Diary Responses to Each of the SAQ AF Questions

<table>
<thead>
<tr>
<th>Expected Diary Range</th>
<th>$n$</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4 times a day</td>
<td>≥28</td>
<td>20.7 (7.5)</td>
<td>24.5 (13.3–25.7)</td>
</tr>
<tr>
<td>1–3 times a day</td>
<td>7 to 21</td>
<td>10.4 (5.5)</td>
<td>9.3 (6.5–13.5)</td>
</tr>
<tr>
<td>≥3 times a week but not every day</td>
<td>3–6</td>
<td>5.3 (3.3)</td>
<td>4.5 (3.3–6.7)</td>
</tr>
<tr>
<td>1–2 times per week</td>
<td>1–2</td>
<td>3.4 (2.7)</td>
<td>2.5 (1.8–4.0)</td>
</tr>
<tr>
<td>Less than once per week</td>
<td>&gt;0 to &lt;1</td>
<td>2.4 (4.0)</td>
<td>1.3 (0.8–2.5)</td>
</tr>
<tr>
<td>None in the last 4 wk</td>
<td>0</td>
<td>1.3 (1.8)</td>
<td>1.0 (0.0–1.8)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; and SAQ AF, Seattle Angina Questionnaire angina frequency.

![Image](http://circoutcomes.ahajournals.org/)

**Figure 2.** Distribution of diary responses of weekly frequency of angina (A) and sublingual nitroglycerin (SL NTG) use (B) by response to Seattle Angina Questionnaire angina frequency (SAQ AF) questions. Three outliers were removed (1 from A and 2 from B) to allow for better visualization of the distributions of diary responses at the lower frequencies of SAQ-reported angina/NTG.
−0.43 to −0.32). Although there was a consistent stepwise relationship between the change reported on the SAQ and the change reported in the diary, some minor discrepancies were observed. For example, among the patients whose SAQ scores did not change, the diary suggested a slight decrease in angina of 1.2 fewer episodes and 0.7 fewer SL NTG used per week. The correlations between change in SAQ AF scores and change in diary entries were similar by age, sex, geographic region, and treatment (Table 3).

### Discussion

In a multinational cohort of patients with stable angina, SAQ AF scores were significantly correlated cross-sectionally, both as individual questions and as an overall domain score, with daily diary entry of angina frequency and SL NTG use. These correlations were consistent regardless of age, sex, or geographic region. Longitudinally, changes in SAQ AF scores were also correlated with changes in diary angina frequency and SL NTG use in the overall population. These findings further support the use of the SAQ as an outcome in clinical care, in registries, and in clinical trials of treatments that are designed to assess cardiac patients’ angina symptoms.

Medical and interventional therapies for ischemic heart disease are designed to either improve survival, quality of life, or both. Clinical trials investigating the effectiveness of therapies that might improve survival use outcomes such as mortality or other surrogate outcomes that are expected to be along the pathway of mortality, such as myocardial infarction. Trials designed to investigate the effectiveness of therapies that improve the quality of life of patients with ischemic heart disease rely on patient-reported outcomes. Although many trials of antianginal medications have relied on treadmill testing or ambulatory ECG monitoring to measure efficacy (by reducing ECG-documented ischemia), these assessments are not necessarily clinically meaningful from the perspective of either the patient or the treating physician. In contrast, patients’ experiences of symptomatic angina are clearly meaningful to both patients and their physicians, given that symptom eradication is a primary goal of therapy.

Although it is technically feasible to measure the burden of angina and the impact of treatments on this burden using either paper or electronic diaries that capture angina frequency on a daily basis, these methods have important limitations. Studies using traditional paper diaries can be limited by inappropriate input of multiple entries in a single sitting (ie, hoarding) and low subject compliance. Daily electronic diaries are more reliable, because they prevent hoarding, and have been shown to be feasible across many countries with observed compliance rates as high as 96% (as it was for TERISA). However, this can be costly because each patient must be provided with an electronic device and data must be handled by an external vendor (eg, the total cost of the electronic diaries in TERISA was $910 987) and is impractical for quality assessment purposes in routine clinical care. Moreover, forgetting to report one’s experiences for a day or more results in missing data, which can be particularly important if the reason that the entry was missed was associated with patients’ symptoms (eg, patients being more likely to complete the diaries on days that they experience angina). Although compliance with daily diary entries in TERISA was high, it is important to note that the run-in period was designed to select patients who were compliant, and the duration of monitoring was short. Furthermore, the patients knew that they were in a clinical trial that relied on these measures and had close monitoring.
and encouragement from the sites. Given their ease of use, questionnaires, such as the SAQ, can be particularly useful for evaluating the burden of angina. Given the findings of this study, we think that the SAQ is a reliable substitute for angina diaries, particularly in long-term studies, or clinical practice, where diaries are less feasible.

One potential limitation to the SAQ is the decreased precision compared with diary reports. Because the SAQ asks about an average during the past 4 weeks, each response item is associated with a potential range of diary results. For example, if a patient responds that they have had chest pain ≥3 times a week but not every day, this would correspond to a diary range of anywhere from 3 to 6 episodes of angina per week. As such, a difference of 3 versus 4 episodes/week may not be detected in the SAQ (eg, when a treatment has a modest effect on angina) but could be detected with an angina diary. There is also a possibility of a floor effect among the few patients who have exceedingly frequent angina. For example, a patient having 20 episodes of angina/d whose angina is reduced by half to 10 episodes/d would be expected to have SAQ score of 0 at both time points, indicating ≥4 episodes/d. In these circumstances, diary data may be more useful to more accurately quantify patients’ angina frequency.

Another important observation from this study is the empirical evidence that patient can, in fact, use a 4-week recall period to assess their angina. The Food and Drug Administration Study Endpoints and Labeling Development (FDA SEALD) group has taken the position that patients are unable to recall accurately their health status over time and that daily assessments are much more accurate in assessing the impact of a new treatment than a questionnaire that has a 4-week (or even a 1-week) recall period. The issue on recall bias is particularly important with an episodic symptom, such as angina. Patients may get angina only when they exert themselves to a level where their myocardial oxygen demand exceeds their supply but may not do that level of exertion every day. It is common in clinical practice for a patient to say “I’ve had no chest pain this week, but 2 weeks ago I had it 3 times.” To address this, the SAQ was constructed with a 4-week recall period so that patients could average or integrate their symptoms over the past month to provide a more accurate assessment of their recent symptom burden. The TERISA study provided a unique opportunity to compare directly a daily angina diary with the SAQ’s 4-week recall period. Finding the strongest correlations with the daily diary averages over 4 weeks (Table II in the Data Supplement) provides empirical support that a 4-week recall period is reasonable for a patient-reported outcome of angina.

Our study should be viewed in light of the following potential limitations. First, the TERISA trial included only angina patients with T2DM. However, there is no a priori reason to expect that patients with T2DM would answer the SAQ questions or diaries in a manner different than patients without T2DM. Second, although the TERISA trial was multinational and there were minimal differences in the correlations of the SAQ with diary data across geographic regions, a minority of patients were enrolled from the United States. Third, it is possible that by having the patients record their angina in a daily diary made them more aware of their burden of angina and consequently increased the accuracy of the SAQ. Finally, we did not examine the other domains of the SAQ because we did not have diary data that corresponded to those domains of health status.

In conclusion, using a large, multinational cohort of patients with T2DM and stable angina, we found that the SAQ AF domain was significantly correlated both cross sectionally and longitudinally with daily diary entry of angina frequency and SL NTG use. These results were consistent regardless of age, sex, or geographic region. These data further support the validity of the SAQ AF domain and should support its continued use as a clinically relevant outcome for clinical trials of therapies that are designed to reduce angina and improve quality of life. Because of the ease of administration, compared with diaries, the SAQ is particularly well suited for studies with longer time frames of analysis, clinical care, and quality assessment/improvement efforts.

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Disclosures

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References


Comparison of the Seattle Angina Questionnaire With Daily Angina Diary in the TERISA Clinical Trial

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