Quality of Life With Ivabradine in Patients With Angina Pectoris
The Study Assessing the Morbidity–Mortality Benefits of the \( I_f \) Inhibitor Ivabradine in Patients With Coronary Artery Disease Quality of Life Substudy

Michal Tendera, MD; Olivier Chassany, MD, PhD; Roberto Ferrari, MD; Ian Ford, PhD; Philippe Gabriel Steg, MD; Jean-Claude Tardif, MD; Kim Fox, MD; on behalf of the SIGNIFY Investigators

**Background**—To explore the effect of ivabradine on angina-related quality of life (QoL) in patients participating in the Study Assessing the Morbidity–Mortality Benefits of the \( I_f \) Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY) QoL substudy.

**Methods and Results**—QoL was evaluated in a prespecified subgroup of SIGNIFY patients with angina (Canadian Cardiovascular Society class score, \( \geq 2 \) at baseline) using the Seattle Angina Questionnaire and a generic visual analogue scale on health status. Data were available for 4187 patients (2084 ivabradine and 2103 placebo). There were improvements in QoL in both treatment groups. The primary outcome of change in physical limitation score at 12 months was 4.56 points for ivabradine versus 3.40 points for placebo \((E, 0.96; 95\% \text{ confidence interval}, -0.14 \text{ to } 2.05; P=0.085)\). The ivabradine–placebo difference in physical limitation score was significant at 6 months \((P=0.048)\). At 12 months, the visual analogue scale and the other Seattle Angina Questionnaire dimensions were higher among ivabradine-treated patients, notably angina frequency \((P<0.001)\) and disease perception \((P=0.006)\). Patients with the worst QoL at baseline (ie, those in the lowest tertile of score) had the best improvement in QoL for 12 months, with improvements in physical limitation and a significant reduction in angina frequency \((P=0.034)\). The effect on QoL was maintained over the study duration, and ivabradine patients had better scores on angina frequency at every visit to 36 months.

**Conclusions**—Treatment with ivabradine did not affect the primary outcome of change in physical limitation score at 12 months. It did produce consistent improvements in other self-reported QoL parameters related to angina pectoris, notably in terms of angina frequency and disease perception.

**Clinical Trial Registration**—URL: http://www.isrctn.com. Unique identifier: ISRCTN61576291.

Key Words: angina pectoris ■ coronary artery disease ■ ivabradine ■ quality of life ■ therapeutics

Chronic stable angina has a major negative effect on health-related quality of life (QoL) because of pain, limited exercise tolerance, and poor general health status.\(^1\)–\(^3\) Angina causes disability and impairment of QoL at a relatively younger age than other cardiovascular diseases, such as heart failure. Moreover, despite widespread use of coronary revascularization, the rate of disability related to angina is increasing; in one report, the years lived with disability increased by 11% from 1990 to 2010.\(^4\) The symptomatic management of angina is expected to improve QoL by reducing the severity or frequency of angina symptoms. Indeed, angina relief is a major goal of treatment for stable coronary artery disease (CAD), and in this sense, quantifying the burden of angina from the perspective of the patient should be regarded as important.
**WHAT IS KNOWN**

- Chronic stable angina has a detrimental effect on quality of life and is expected to be improved by symptomatic treatment.
- Ivabradine is an antianginal agent.

**WHAT THE STUDY ADDS**

- The Study Assessing the Morbidity–Mortality Benefits of the 
  I, Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY) Quality of Life Substudy used the Seattle Angina Questionnaire to explore the effect of ivabradine on quality of life in 4187 patients with angina.
- Although the substudy did not reach its primary outcome of improvement in physical limitation at 12 months, treatment with ivabradine did improve other measures of quality of life related to symptoms and disease perception for 6 to 12 months, with an effect on angina frequency persisting up to 3 years.
- Patients in the lowest tertile for angina frequency score at baseline had the best ivabradine-associated improvement in quality of life for 12 months.

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- The Study Assessing the Morbidity–Mortality Benefits of the I, Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY) trial included 19102 patients with CAD without clinical heart failure who received ivabradine up to a dosage of 10 mg BID or placebo. The main results were neutral with no effect of treatment on the primary composite end point of cardiovascular death or nonfatal myocardial infarction over a median follow-up of 27.8 months ($P$=0.20).5 The use of ivabradine was associated with an increase in the incidence for primary composite end point in a prespecified subgroup of 12049 patients with Canadian Cardiovascular Class (CCS) class II or higher angina at baseline ($P$=0.02). Analyses of the antianginal effect of ivabradine in the same angina subgroup were in line with the symptomatic use of the agent in patients with stable angina pectoris. There were improvements in CCS angina class versus placebo ($P$=0.01) and a trend toward lower incidence of elective coronary revascularization ($P$=0.058).5

In this article, we present the results of the SIGNIFY QoL substudy, in which the Seattle Angina Questionnaire (SAQ) and a visual analogue scale (VAS) were used to assess the effect of treatment with ivabradine on angina-related QoL.

**Methods**

**Study Design and Patients**

SIGNIFY was a randomized, double-blind, placebo-controlled trial in patients with stable CAD without clinical heart failure. The design and results of SIGNIFY have been described elsewhere.5,6 The protocol of the study was approved by the ethics committee at each participating institution, and all patients gave written informed consent before entry to the study. Briefly, SIGNIFY included 19102 patients with documented stable CAD, a heart rate of 70 bpm or higher in sinus rhythm, and at least 1 major or 2 minor adverse prognostic factors. A prespecified subgroup of 12049 patients had CCS angina class II or higher at baseline. The presence of angina in this subgroup would be expected to have a substantial effect on QoL and constituted the basis for the QoL substudy population for exploration of the effect of ivabradine treatment on QoL.

After a 2- to 4-week placebo run-in, all participants were randomly allocated to receive ivabradine at a dose of 7.5 mg BID or matching placebo (except for those aged $\geq$75 years who received 5.0 mg BID). Randomization was stratified by center and angina status. At every visit, dosage was adjusted (5, 7.5, or 10 mg BID) to a target heart rate of 55 to 60 bpm. Treatment was stopped if the heart rate was $<45$ bpm on the lowest dosage or persisted at $<50$ bpm for 1 week and in case of symptomatic bradycardia. In addition, all patients received stable background therapy according to guidelines in force at the time of inclusion.5

Countries for which a validated version of the SAQ was available in the local language(s) could participate in the SIGNIFY QoL substudy, in which the Seattle Angina Questionnaire (SAQ) and a visual analogue scale (VAS) were used to assess the effect of treatment with ivabradine on angina-related QoL.

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substudy. All centers in each selected country were invited to participate in the substudy, and all patients in those centers with symptoms of angina at baseline (CCS angina class II or higher) were invited to participate in the substudy. Substudy patients gave specific informed consent for the QoL substudy in addition to that for the main study.

**QoL Questionnaire**

QoL was assessed using the SAQ, as well as a generic VAS at baseline, 6, 12, 24, and 36 months and last visit, to record the patient’s evaluation of his or her own health status. At each substudy visit, the patients self-administered the SAQ and the VAS before the other investigations related to the main study, to avoid any influence of the subsequent discussion with the physician who was not aware of the QoL data reported by the patient.

The SAQ is a validated 19-item questionnaire that measures 5 dimensions (physical limitation, angina frequency, disease perception, angina stability, and treatment satisfaction) to evaluate QoL specifically in angina populations. SAQ scores were calculated by summing items within a dimension and transforming them to a 0 to 100 graded scale. For all dimensions, a higher score indicates better health status or satisfaction. Quality control measures were implemented for both the SAQ and VAS to confirm their reliability and validity independently of the treatment group in the substudy population.

The primary end point was the change from baseline at 12 months in the physical limitation dimension of the SAQ; this was selected as the primary end point because it was considered essential to measure the most direct functional effect of angina. Secondary end points included 12-month change in the angina frequency, as well as 12-month changes, in the other SAQ dimensions and the VAS.

Analyses were also carried out in subgroups defined according to the baseline characteristics of heart rate (<75 or ≥75 bpm), age (<65 or ≥65 years), CCS class of angina (class II or class III/IV), sex, and use of β-blockers at randomization (yes/no). The change in QoL over the duration of the study was also assessed by plotting QoL parameters at 6, 12, 24, and 36 months. A complementary analysis, including a comparison of the proportion of patients with changes deemed as clinically relevant, was performed to assess the effect of treatment on change in QoL in the population divided according to tertiles of baseline physical limitation score and angina frequency score. A change in physical limitation score of ≥8 points or a change in angina frequency score of ≥20 points was considered as clinically significant. Similarly, changes in disease perception, treatment satisfaction, and angina stability were considered as clinically significant if they were 16, 12, and ≥25 points, respectively.

### Statistical Methods

It was estimated that a sample size of 4500 patients would allow detection of a between-group difference on the SAQ physical limitation dimension (effect size of 0.15, 95% power using a 2-sided test, and 5% type I error).

Baseline characteristics are presented as mean (SD) for continuous variables and counts (percentages) for categorical variables in the substudy population. All analyses are performed on a population comprised of randomized patients included in the QoL substudy with baseline CCS class II or higher with a record of physical limitation on the SAQ at baseline and at least 1 postbaseline evaluation during the first 12 months of follow-up and who had taken at least 1 dose of study treatment. Missing QoL follow-up data were dealt with using the last observation-carried-forward method; patients who died were attributed a score of 0 at the next scheduled visit. The difference between ivabradine and placebo on change in QoL was estimated using a parametric ANCOVA with country as a random effect and baseline and country and presented as P values. All statistical analyses were performed using SAS software (version 9.2).

### Results

The substudy included 5231 patients (2618 ivabradine and 2613 placebo) in 591 centers in 35 countries. Of these, 4187 patients (2084 ivabradine and 2103 placebo) had CCS class

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**Table 1. Baseline Characteristics in the Study Assessing the Morbidity–Mortality Benefits of the I Inhibitor Ivabradine in Patients With Coronary Artery Disease (SIGNIFY) Quality of Life Substudy Population**

<table>
<thead>
<tr>
<th>Analyzed Population (n=4187)</th>
<th>Ivabradine (n=2084)</th>
<th>Placebo (n=2103)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>64.1±6.8</td>
<td>64.1±7.1</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.1±4.4</td>
<td>29.0±4.6</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76.9±6.7</td>
<td>77.2±6.9</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>1492 (72)</td>
<td>1512 (72)</td>
</tr>
<tr>
<td>Ethnic origin, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1915 (92)</td>
<td>1933 (92)</td>
</tr>
<tr>
<td>Asian</td>
<td>114 (5)</td>
<td>101 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>54 (3)</td>
<td>67 (3)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mmHg</strong></td>
<td>130.0±12.7</td>
<td>129.9±12.7</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mmHg</strong></td>
<td>78.5±7.9</td>
<td>78.5±7.6</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors and medical history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease duration, y</td>
<td>6.8±6.3</td>
<td>6.8±6.3</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>1624 (78)</td>
<td>1656 (79)</td>
</tr>
<tr>
<td>Previous coronary revascularization, n (%)</td>
<td>1127 (54)</td>
<td>1140 (54)</td>
</tr>
<tr>
<td>CCS class II angina or higher, n (%)</td>
<td>2084 (100)</td>
<td>2103 (100)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>1419 (68)</td>
<td>1448 (69)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>718 (34)</td>
<td>742 (35)</td>
</tr>
<tr>
<td>Peripheral artery disease, n (%)</td>
<td>352 (17)</td>
<td>382 (18)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>429 (21)</td>
<td>484 (23)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1845 (88)</td>
<td>1869 (89)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>55.3±8.0</td>
<td>55.1±8.2</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>136 (7)</td>
<td>128 (6)</td>
</tr>
<tr>
<td>Concomitant treatments, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet or anticoagulants</td>
<td>2041 (98)</td>
<td>2048 (97)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1899 (91)</td>
<td>1907 (91)</td>
</tr>
<tr>
<td>Statins</td>
<td>1928 (93)</td>
<td>1927 (92)</td>
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<tr>
<td>β-blockers</td>
<td>1802 (86)</td>
<td>1842 (88)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>1358 (65)</td>
<td>1364 (65)</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>413 (20)</td>
<td>401 (19)</td>
</tr>
<tr>
<td>Dihydralpydine CCB</td>
<td>505 (24)</td>
<td>509 (24)</td>
</tr>
<tr>
<td>Organic nitrates</td>
<td>1161 (56)</td>
<td>1116 (53)</td>
</tr>
<tr>
<td>Diltiazem or verapamil</td>
<td>93 (4)</td>
<td>97 (5)</td>
</tr>
<tr>
<td>Antidiabetic agents</td>
<td>629 (30)</td>
<td>651 (31)</td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%). There were no significant differences between the treatment groups in any of the baseline characteristics at P<0.05. ACE indicates angiotensin-converting enzyme; CCB, calcium-channel blocker; and CCS, Canadian Cardiovascular Society.
II or higher angina, had received at least 1 dose of study treatment, and had at least 1 baseline and 1 postbaseline evaluation of physical limitation score on the SAQ during the first 12 months (Figure 1). The SAQ and VAS were fully completed at baseline in 4064 (97%) and 4111 patients (98%), respectively. The main reason for not completing the QoL evaluation at any postbaseline visit for ongoing patients was center mistake (24%) or the patient not attending the visit or only being contacted by telephone (39%). Center mistake was the reason given for not completing the evaluation in 67% of cases at 6 months; subsequently, reminders were sent to investigators, and center mistake was a less common reason for the rest of the trial (17% at 3 years). The median follow-up of the substudy patients was 35.4 months in the ivabradine group and 35.3 months in the placebo group. The mean dosage of ivabradine in that treatment group was 8.24±1.77 mg BID.

There were no differences between the 2 treatment groups at baseline (Table 1), and there were no relevant differences in the substudy population compared with the patients with angina in the main study.5 The mean age of the population was 64.1±7.0 years, and 72% were men. The mean heart rate at baseline was 77.0±6.8 bpm. More than 3 quarters of the population had previously had a myocardial infarction (78%), and half (54%) had coronary revascularization. The patients were receiving guideline-recommended background therapy for their angina, including β-blockers (87%), diltiazem (24%), and organic nitrates (54%). At baseline, mean physical limitation score was 61.12±19.71, and angina frequency score was 67.32±21.43. Patients in the ivabradine group were more likely to move to a lower CCS class (25% of ivabradine patients had an improvement at 3 months versus 17% of placebo patients; P<0.0001; this effect was consistent at 12, and 24 months; P<0.0001, P=0.0001, and P=0.006, respectively).

QoL improved during 12 months in placebo patients, as well as in ivabradine patients (Table 2). The primary outcome of change in physical limitation score at 12 months was 4.56 points in the ivabradine group versus 3.40 points in the placebo group (E, 0.96; 95% CI, −0.14 to 2.05; P=0.085; Figure 2). There was evidence of an early effect of ivabradine on physical limitation dimension with a significant treatment–placebo difference at 6 months (E, 1.04; 95% CI, 0.01−2.07; P=0.048). There were significant ivabradine-placebo differences on the other SAQ dimensions and the VAS at 12 months (Table 2; Figure 2). Notably, there were significant improvements in the angina frequency and disease perception dimensions with ivabradine versus placebo at 12 months (angina frequency: 11.00 versus 8.48 points, respectively; E, 2.32; 95% CI, 1.17−3.48; P<0.001 and disease perception: 10.57 versus 8.61 points, respectively; E, 1.17; 95% CI, 0.46–2.69; P=0.006). Similar results were found in sensitivity analyses, including unadjusted analyses, an approach that did not involve imputing a score of 0 for those who died and a mixed model with repeated measures (data not shown). Subgroup analyses, including angina class, resting heart rate, β-blocker intake at baseline, sex, and age, showed consistent results in the same direction for physical limitation and angina frequency scores (Figure 3).
In our substudy, 42.5% of ivabradine patients reached the clinically relevant change of ≥8 points in physical limitation score at 12 months versus 41.7% in the placebo group (odds ratio [OR], 1.02; 95% CI, 0.90–1.17; P=0.72). Similarly, 41.0% of ivabradine patients reached a clinically relevant change of ≥20 points in angina frequency score versus 37.7% of the placebo group (OR, 1.20; 95% CI, 1.04–1.38; P=0.012). A clinically significant change in disease perception (≥21 points) was observed in 45.3% of ivabradine patients versus 42.0% of placebo patients (OR, 1.16; 95% CI, 1.01–1.33; P=0.037), whereas a clinically meaningful change in treatment satisfaction (≥12 points) was found in 34.2% of ivabradine patients versus 31.3% of placebo patients (OR, 1.10; 95% CI, 0.94–1.28; P=0.24). Finally, more ivabradine patients had a clinically meaningful change in angina stability (≥25 points) than placebo (36.4% versus 32.8%; OR, 1.18; 95% CI, 1.03–1.35; P=0.014). The patients in the lowest tertiles of QoL were more likely to reach a clinically relevant change. In this group, 58.6% of ivabradine patients and 56.0% of placebo patients reached a clinically relevant change in physical limitation (OR, 1.09; 95% CI, 0.88–1.36; P=0.44), and 73.2% versus 64.9%, respectively, reached a relevant change in angina frequency (OR, 1.47; 95% CI, 1.12–1.94; P=0.006).

The change in QoL scores during the 3 years of the study is presented in Figure 4 for angina frequency and VAS scores. An increase in angina-related QoL in the first 6 months of treatment was observed in both groups. The patients in the ivabradine group had higher values for angina frequency score at every visit, which was significantly better with ivabradine at 12, 24, and 36 months. For the VAS, the trend toward better scores with ivabradine was preserved during the whole study duration.

Discussion

There are few published studies of the effect of antianginal treatment on QoL in patients with angina pectoris in the long term. With perhaps the sole exception to date of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, the few trials that have reported QoL in CAD populations are generally short term, small scale, and uncontrolled. At 6 months, there was a significant improvement in physical limitation with ivabradine, with a nonsignificant trend persisting after 12 months. In all other SAQ dimensions, as well as in the health status assessed.
Failure.10–12 Treatment with ivabradine was associated with the effect of ivabradine on disease-specific QoL in heart failure. This is remarkable insofar as the SIGNIFY substudy population was lower than the levels that have been reported in other trials in stable CAD and angina pectoris treated according to the guidelines, performed in a well-treated population using a validated disease-specific questionnaire for a long follow-up time. The robustness of our results is demonstrated by the low rate of missing data and the good internal consistency and validity of the scales used. The main limitation is the generalizability of the study findings because the study enrolled patients in sinus rhythm with a heart rate of ≥70 bpm.

The main strength of our study is that with 4187 patients, it is, to our knowledge, the largest assessment of QoL in patients with stable angina pectoris treated according to the guidelines, performed in a well-treated population using a validated disease-specific questionnaire for a long follow-up time. The robustness of our results is demonstrated by the low rate of missing data and the good internal consistency and validity of the scales used. The main limitation is the generalizability of the study findings because the study enrolled patients in sinus rhythm with a heart rate of ≥70 bpm.

In conclusion, this QoL substudy of the SIGNIFY trial was carried out in a large population of patients with stable CAD and symptomatic angina pectoris but without clinical heart failure, who were receiving guideline-recommended background treatment appropriate to their cardiovascular condition. Treatment with ivabradine seems to be associated with improvements in self-reported QoL related to angina pectoris, notably in terms of angina frequency and disease perception.

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Quality of Life With Ivabradine in Patients With Angina Pectoris: The SIGNIFY Quality of Life Substudy

Tendera et al: Quality of Life With Ivabradine in Angina Pectoris

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