Quality of life with ivabradine in patients with angina pectoris:

The SIGNIFY Quality of Life Substudy

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Abstract (250 words)

Background To explore the effect of ivabradine on angina-related quality of life (QoL) in patients participating in the SIGNIFY Quality of Life substudy.

Methods and results QoL was evaluated in a prespecified subgroup of SIGNIFY patients with angina (Canadian Cardiovascular Society class ≥2 at baseline) using the Seattle Angina Questionnaire (SAQ) and a generic visual analogue scale (VAS) on health status. Data were available for 4187 patients (2084 ivabradine, 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% CI, –0.13– 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 VAS and the other SAQ 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 (i.e. those in the lowest tertile of score) had the best improvement in QoL over 12 months, with improvements in the 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.

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

Clinical trial registration ISRCTN61576291.

Keywords: ivabradine; quality of life; angina; SIGNIFY; SAQ

Introduction

Chronic stable angina has a major negative impact on health-related quality of life (QoL) due to 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 and/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 very important.

The SIGNIFY (Study Assessing the Morbidity–Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease) trial included 19 102 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 endpoint 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 endpoint in a prespecified subgroup of 12 049 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 towards lower incidence of elective coronary revascularization (p=0.058).[5] In this article, we present the results of the SIGNIFY Quality of Life 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 prior to entry to the study. Briefly, SIGNIFY included 19 102 patients with documented stable CAD, a heart rate of 70 bpm or higher in sinus rhythm, and at least one major or two minor adverse prognostic factors. A prespecified subgroup of 12 049 patients had CCS angina class II or higher at baseline. The presence of angina in this subgroup would be expected to have a substantial impact 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 75 years or older, 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 less than 45 bpm on the lowest dosage, or persisted at less than 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. 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.

Quality of life questionnaire

QoL was assessed using the SAQ, as well as a generic visual analogue scale (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.[7] 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 treatment group in the substudy population.

The primary endpoint was change from baseline at 12 months in the physical limitation dimension of the SAQ; this was selected as the primary endpoint since it was considered essential to measure the most direct functional impact of angina. Secondary endpoints 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), gender, and use of beta-blockers at randomization (Yes/No). The change in quality of life 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 more or a change in angina frequency score of 20 points or more were considered as clinically significant.[8] Similarly, changes in disease perception, treatment satisfaction, and angina stability were considered as clinically significant if they were 16, 12, and 25 points or more, 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 two-sided test, and 5% type I error).

Baseline characteristics are presented as means (SD) for continuous variables and counts (percentages) for categorical variables in the substudy population. All analyses are presented in 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 one postbaseline evaluation during the first 12 months of follow-up, and who had taken at least one 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 zero at next scheduled visit. The difference between ivabradine and placebo on change in QoL was estimated using a parametric covariance analysis with country as a random effect and baseline as a covariate. Results are presented as estimates (E) with associated standard errors (SEs), two-sided 95% confidence intervals (CI), and p values. A range of sensitivity analyses were carried out, including unadjusted analyses, an analysis that did not involve imputing a score of zero for those who died, and a mixed model with repeated measures. The proportions of patients with clinically relevant changes were compared using a logistic regression adjusted for 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, 2613 placebo) in 591 centers in 35 countries. Of these, 4187 patients (2084 ivabradine, 2103 placebo) had CCS class II or higher angina, had received at least one dose of study treatment, and had at least one baseline and one 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 reasons 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%). Centre 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 two treatment groups at baseline (**Table 1**), and there were no relevant differences in the substudy population compared with the angina patients in the main study.[5] The mean age of the population was 64.1±7.0 years and 72% were male. Mean heart rate at baseline was 77.0±6.8 bpm. More than three-quarters of the population had previously had a myocardial infarction (78%) and half (54%) coronary revascularization. The patients were receiving guideline-recommended background therapy for their angina, including beta-blockers (87%), dihydropyridine calcium channel blockers (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 6, 12, and 24 months, p<0.0001, p=0.0001, and p=0.006, respectively).

QoL improved over 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, –0.13– 2.05, p=0.085) (**Figure 2**). There was evidence of an early impact of ivabradine on physical limitation dimension with a significant treatment-placebo difference at 6 months (E, 1.04, 95% CI, 0.01 to 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: 11.01 versus 8.48 points, respectively, E, 2.32, 95% CI, 1.17 to 3.48, p<0.001; disease perception: 10.57 versus 8.61 points, respectively, E, 1.57, 95% CI, 0.46 to 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 zero for those who died, and a mixed model with repeated measures (data not shown). Subgroup analyses including angina class, resting heart rate, and beta-blocker intake at baseline, sex and age showed consistent results in the same direction for physical limitation and angina frequency scores (**Figure 3**).

Patients with the worst QoL at baseline (i.e. those in the lowest tertile of score at baseline) generally had the best improvement in QoL over 12 months. The patients in the lowest tertile of physical limitation score at baseline (1344 patients, score <52.78

points) had a clinically significant increase by 13.44 points in the ivabradine group at 12 months and 12.04 points in the placebo group (E, 1.12, 95% CI, –1.04 to 3.27, p=0.31). Similarly, the patients in the lowest tertile of angina frequency score at baseline (979 patients, score <60 points) had the greatest and clinically significant improvement at 12 months (increases of 27.72 and 24.47 points, respectively) with a significant between-group difference in favor of ivabradine (E, 3.06, 95% CI, 0.23 to 5.89, p=0.034).

In our substudy, 42.5% of ivabradine patients reached the clinically relevant[8] change of 8 points or more in physical limitation score at 12 months versus 41.7% in the placebo group (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 or more 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 (≥16 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), while 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 over the 3 years of the study is presented in **Figure 4** for angina frequency and VAS scores. An increase in angina-related quality of life 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 towards better scores with ivabradine was preserved over the whole study duration.

Discussion

There are few published studies of the impact of antianginal treatment on QoL in patients with angina pectoris in the long-term. With perhaps the sole exception to date of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial,[9] 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 non-significant trend persisting after 12 months. In all other SAQ dimensions as well as in the health status assessed by VAS at the 12 month follow-up, patients in the ivabradine group fared significantly better than those on placebo. Thus, our results indicate that antianginal treatment with ivabradine has a positive effect on a range of QoL indices in patients with angina, despite of the lack of the long-term effect on physical limitation.. This is remarkable insofar as the SIGNIFY population had stable disease, for which they were receiving a good level of background antianginal therapy, and had no indication for revascularization at study entry, implying that their quality of

life was acceptable at the outset of the study. Our findings are also in line with previous smaller scale studies with ivabradine in angina, and also with larger-scale studies of the effect of ivabradine on disease-specific QoL in heart failure.[10-12] Treatment with ivabradine was associated with an improvement of angina frequency score and disease perception versus placebo ($p<0.001$ and $p=0.006$, respectively). Moreover, the improved QoL in the ivabradine group was consistent at 12 months for all SAQ dimensions, the evaluation of health status VAS, and also for all of the predefined subgroups. The effect of ivabradine on angina frequency and VAS did not attenuate with time over the 3 years of the study.

The SAQ changes observed in the global QoL SIGNIFY substudy population were lower than the levels that have been designated elsewhere as clinically relevant.[8] On the other hand, in our study, more ivabradine patients reached clinically relevant changes in angina frequency, disease perception and treatment satisfaction scores than in the placebo group, with highly significant results for angina frequency in patients in the lowest tertile of QoL. QoL is a multidimensional assessment, and subjective experience of QoL can vary between individuals and be difficult to measure on the scale of a large population such as ours. It may therefore be difficult to show large differences over the long term (12 months), especially against a background of a strong natural tendency to improve in the placebo group.[13] QoL data are important since they give a measure of the disease experience perceived by the patient, in terms of well-being, functional status, productivity, and the side effects of treatments; an impact on QoL may sometimes be regarded as more important than effects on clinical outcomes.[14] Indeed, the aim of any antianginal treatment is to improve symptoms, and it cannot be assumed that this reflects an improvement in outcomes.[5,15,16] In this

context, we should also note that the QoL values in SIGNIFY at baseline were similar or better than values reported in other trials in stable CAD and angina (COURAGE and the Efficacy of Ranolazine in Chronic Angina [ERICA] trial),[9,17] in patients who were either awaiting coronary angioplasty or suffering from severe angina (more than 3 attacks per week). This may also make it more difficult to show a large improvement.

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 over 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 since the study enrolled patients in sinus rhythm with heart rate of 70 bpm or higher.

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 appears 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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Conflict of interest disclosures

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Figure legends

Figure 1. Trial profile.

Other reasons were generally nonmedical, including consent withdrawal or treatment refusal. Patients could have more than one reason for exclusion.

Figure 2. Effect of treatment with ivabradine from baseline to 12 months on quality life on the Seattle Angina Questionnaire (SAQ) and a visual analogue scale.

Values are estimates (E) of the adjusted difference between group means (ivabradine – placebo) and 95% confidence interval (CI).

Figure 3. Effect of treatment with ivabradine on quality life on the Seattle Angina Questionnaire (SAQ) from baseline to 12 months in subgroups divided according to baseline characteristics for the physical limitation score and the angina frequency score.

Values are estimates (E) of the adjusted difference between group means (ivabradine – placebo) and 95% confidence interval (CI). Patient numbers are given for physical limitation score.

Figure 4. Angina frequency score (**A**) on the Seattle Angina Questionnaire (SAQ) and health status on the visual analogue scale (VAS) (**B**) over the 3 years in the substudy population.

p values for ivabradine-placebo difference from a covariance analysis using the last observation carried forward method for the management of missing data.

Table 1. Baseline characteristics in the SIGNIFY Quality of Life Substudy population.

Values are means±SD or n (%). There were no significant differences between the treatment groups in any of the baseline characteristics at $p<0.05$. ACE=angiotensin converting enzyme. CCB=calcium channel blocker. CCS=Canadian Cardiovascular Society.

	Analyzed population (N=4187)	
	Ivabradine (n=2084)	**Placebo (n=2103)**
Demographic characteristics		
Age (years)	64.1±6.8	64.1±7.1
Body mass index (kg/m^2)	29.1±4.4	29.0±4.6
Heart rate (bpm)	76.9±6.7	77.2±6.9
Male	1492 (72%)	1512 (72%)
Ethnic origin		
• Caucasian	1915 (92%)	1933 (92%)
• Asian	114 (5%)	101 (5%)
• Other	54 (3%)	67 (3%)
Systolic blood pressure (mm Hg)	130.0±12.7	129.9±12.7
Diastolic blood pressure (mm Hg)	78.5±7.9	78.5±7.6
Cardiovascular risk factors and medical history		
Coronary artery disease duration (years)	6.8±6.3	6.8±6.3
Previous myocardial infarction	1624 (78%)	1656 (79%)
Previous coronary revascularization	1127 (54%)	1140 (54%)
CCS class II angina or higher	2084 (100%)	2103 (100%)
Dyslipidemia (%)	1419 (68%)	1448 (69%)
Diabetes mellitus (%)	718 (34%)	742 (35%)
Peripheral artery disease (%)	352 (17%)	382 (18%)
Current smoker (%)	429 (21%)	484 (23%)
Hypertension (%)	1845 (88%)	1869 (89%)
Left ventricular ejection fraction (%)	55.3±8.0	55.1±8.2
Previous stroke (%)	136 (7%)	128 (6%)
Concomitant treatments		
Antiplatelet or anticoagulants	2041 (98%)	2048 (97%)
Aspirin	1899 (91%)	1907 (91%)
Statins	1928 (93%)	1927 (92%)
Beta-blockers	1802 (86%)	1842 (88%)
ACE inhibitors	1358 (65%)	1364 (65%)
Angiotensin II receptor blockers	413 (20%)	401 (19%)
Dihydropyridine CCB	505 (24%)	509 (24%)
Organic nitrates	1161 (56%)	1116 (53%)
Diltiazem or verapamil	93 (4%)	97 (5%)
Antidiabetic agents	629 (30%)	651 (31%)

Table 2. Quality of life results at 12 months on Seattle Angina Questionnaire (5 dimensions) and health status on the visual analogue scale (VAS) in patients with baseline CCS class II or higher angina in patients with data.

Values are means±SD or estimates (E) of the hazard ratio (ivabradine /placebo) with 95% confidence intervals (CI). LOCF= last observation carried forward. Adjusted for country and baseline value. Numbers of patients: [a]2056 ivabradine; 2081 placebo. [b]2075 ivabradine; 2090 placebo. [c]2040 ivabradine; 2067 placebo.[d]2075 ivabradine; 2100 placebo. [e]2042 ivabradine; 2056 placebo.

	Ivabradine (N=2084)	Placebo (N=2103)
Physical limitation		
• Baseline	60.86±19.90	61.38±19.52
• 12 months (LOCF)	65.42±21.55	64.78±21.52
• Difference 12 months - baseline	4.56±19.92	3.40±19.99
• E (95% CI), p value	0.96 (–0.14–2.05), p=0.085	
Angina frequency[a]		
• Baseline	67.09±21.66	67.50±21.18
• 12 months (LOCF)	78.09±20.99	75.98±22.06
• Difference 12 months - baseline	11.00±22.12	8.47±22.81
• E (95% CI), p value	2.32 (1.17–3.48), p<0.001	
Disease perception[b]		
• Baseline	55.25±20.52	55.87±20.64
• 12 months (LOCF)	65.83±20.34	64.48±20.20
• Difference 12 months - baseline	10.57±22.37	8.61±22.21
• E (95% CI), p value	1.57 (0.46–2.69), p=0.006	
Angina stability[c]		
• Baseline	57.77±18.69	58.71±19.30
• 12 months (LOCF)	64.11±23.28	62.63±23.25
• Difference 12 months - baseline	6.34±28.18	3.92±28.69
• E (95% CI), p value	1.61 (0.20–3.02), p=0.025	
Treatment satisfaction[d]		
• Baseline	80.81±15.85	81.85±15.34
• 12 months (LOCF)	85.30±15.92	84.59±16.64
• Difference 12 months - baseline	4.49±17.80	2.74±18.05
• E (95% CI), p value	1.13 (0.22–2.04), p=0.015	
VAS[e]		
• Baseline	62.52±15.97	62.74±15.91
• 12 months (LOCF)	68.26±16.56	67.44±16.70
• Difference 12 months - baseline	5.75±17.41	4.70±18.17
• E (95% CI), p value	0.95 (0.03–1.86), p=0.044	