Effects of Ranolazine on Disease-Specific Health Status and Quality of Life Among Patients With Acute Coronary Syndromes
Results from the MERLIN-TIMI 36 Randomized Trial

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Background—Ranolazine has been shown to reduce myocardial ischemia and symptom severity among selected patients with chronic angina. However, data regarding the effect of ranolazine on health status/quality of life (QOL) are limited.

Methods and Results—We performed a prospective QOL analysis alongside the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-elevation acute coronary syndromes (MERLIN)-TIMI 36 trial, a randomized, double-blind, placebo-controlled trial of ranolazine in 6560 patients with non–ST-elevation acute coronary syndromes. Health status/QOL was evaluated at baseline and 4, 8, and 12 months after index hospitalization using the Seattle Angina Questionnaire, Rose dyspnea scale, SF-12, and EuroQol-5D. Health status/QOL scores improved significantly at all follow-up time points for both treatment arms. In the overall population, randomization to ranolazine was associated with minimal 12-month improvements in angina frequency and Seattle Angina Questionnaire-QOL ($P<0.05$). In subsequent exploratory analyses, there was a significant interaction between the benefits of ranolazine and anginal status before the index event. Among patients with prior angina ($n=3565$), treatment with ranolazine was associated with modest benefits across the full range of QOL domains, with the greatest benefits observed in angina frequency (mean effect $3.4; P<0.001$) and Seattle Angina Questionnaire-QOL (mean effect $2.7; P<0.004$). There were no significant benefits among patients without prior angina, however.

Conclusion—Among a broad population of patients with unstable coronary disease, ranolazine had a minimal effect on disease-specific health status and QOL over $\approx12$ months of follow-up. Posthoc subgroup analysis, however, suggested a modest benefit among the subgroup of patients with angina before their acute coronary syndromes event. (Circ Cardiovasc Qual Outcomes. 2008;1:00-00.)

Key Words: angina ■ quality of life ■ trials ■ ranolazine

Myocardial ischemia, manifested as angina, substantially impairs functional capacity and overall quality of life (QOL) in patients with coronary artery disease (CAD).\(^1\)\(^-\)\(^3\) Therefore, amelioration of symptoms of myocardial ischemia is a major objective of the management of patients with established CAD.\(^4\) Contemporary approaches to diminish the burden of myocardial ischemia have centered on reducing myocardial oxygen demand through modification of heart rate, cardiac contractility, and ventricular wall tension; combined with interventions designed to improve myocardial oxygen supply by improving coronary blood flow such as antithrombotic therapies, revascularization techniques, and coronary vasodilation.\(^5\) Ranolazine is a piperazine derivative that has been shown to exert anti-ischemic effects in a unique and potentially complementary manner to currently available therapies, without significant hemodynamic effects.\(^6\)\(^-\)\(^8\) It was approved by the US Food and Drug Administration in January 2006 for use in patients with chronic stable angina after having been shown in several trials to improve exercise performance and increase the time to angina/ischemia in this population of patients\(^6\)\(^-\)\(^8\) and to reduce angina frequency among patients with refractory angina.\(^9\)

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dromes (MERLIN)-TIMI 36 trial studied the effects of ranolazine in a broad population of patients with acute coronary syndrome (ACS). Although the primary analysis did not show a benefit of ranolazine on the composite end point of cardiovascular death, myocardial infarction (MI), or recurrent ischemia, the prespecified secondary end point of recurrent ischemia was reduced with ranolazine when compared with placebo (14% versus 16%; P=0.03).10 Because ≈1 in 4 patients continue to experience angina symptoms 1 month after an ACS event,11 we hypothesized that reducing the incidence and severity of myocardial ischemia would be expected to have a significant positive impact on these patients’ symptom burden, functional capability, and overall QOL. To test this hypothesis, we therefore performed a prospective study alongside MERLIN-TIMI 36 to evaluate the short- and long-term benefits of ranolazine on cardiocpecific health status and QOL in a broad population of patients after an ACS event.

Methods

The details of the MERLIN-TIMI 36 trial, including study design and population, treatment protocol, follow-up procedures, and study end points have been described previously.12

Study Population

Between October 2004 and May 2006, 6560 patients underwent randomization at 442 sites in 17 countries. Eligible patients were aged 18 years or older, had symptoms consistent with myocardial ischemia at rest lasting at least 10 minutes and present within the previous 48 hours, and had at least 1 of the following moderate- to high-risk indicators: elevated biomarkers of myocardial necrosis, ST depression of at least 0.1 mV, diabetes mellitus or a TIMI risk score of ≥3.13 Key exclusion criteria included persistent ST-segment elevation, successful revascularization of the culprit stenosis before randomization, and EKG abnormalities that would interfere with interpretation of Holter monitoring for ischemia.

Study Protocol

Eligible patients were randomized to receive either ranolazine or placebo in a 1:1 ratio, with stratification according to the responsible physician’s intended initial management strategy (early invasive versus conservative). Study drug (ranolazine or matching placebo) was administered as 200 mg intravenously more than 1 hour followed by an 80 mg/h intravenous infusion (40 mg/h for patients with creatinine clearance <30 mL/min), which was continued for 12 to 96 hours. On completion of the infusion, oral study drug was initiated at a dose of 1000 mg twice daily. Dose reduction was prespecified for patients with new renal insufficiency or persistent prolongation of the QT-interval. Institutional Research Board approval was obtained at each participating hospital, and informed consent was obtained from all patients before enrollment.

Outcome Measurements

Health status/QOL indicators were collected by means of standardized, written questionnaires at baseline; at 4, 8, and 12 months after the index hospitalization; and at the final study visit (which occurred once the required number of end points had been reached) using a broad range of instruments. Patients who did not attend a follow-up visit were administered the same instruments by structured interview, when possible. Disease-specific health status was assessed using the Seattle Angina Questionnaire (SAQ)14,15 and the Rose dyspnea scale.16 The SAQ is a 19-item questionnaire that measures 5 clinically important dimensions of health in patients with CAD: angina frequency, angina stability, physical limitations, treatment satisfaction, and disease perception/QOL. Each domain has a score ranging from 0 to 100, with higher scores indicating less disease burden. The angina frequency domain quantifies the frequency and burden of angina over the previous 4 weeks. The physical limitations domain measures how daily activities are limited by symptoms of CAD. The treatment satisfaction domain evaluates the level of satisfaction with the treatment of the patient’s angina. The disease perception/QOL domain determines how the patient perceives that CAD is impacting his or her QOL. The angina stability domain was not included in this study because it is a cross-sectional measure of short-term change in health status, which presents challenges in interpretation for longitudinal analyses.14 The SAQ has undergone extensive reliability and validity testing14,15 and has been shown to correlate with long-term survival and ACS hospitalization among patients with chronic CAD.17

The Rose dyspnea scale is a 4-item questionnaire that assesses the patient’s level of dyspnea with common activities (such as dressing or walking at own pace) and has been shown to be sensitive to change in CAD patients.18,19 Each question answered positively is assigned a score of 1 point, and a summary score is generated with scores ranging from 0 to 4, with higher scores indicating more limitation because of dyspnea. Generic health status was measured using the physical and mental components of the Medical Outcomes Study 12-item Short Form (SF-12)20 and the EuroQol-5D, a 5-item instrument assessing specific domains of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.21 The EuroQol-5D results were converted to utility weights according to an algorithm developed for the US population.22,23 As MERLIN-TIMI 36 was a multinational clinical trial, country-specific instruments were used for the health status/QOL assessment. For the instruments for which published translations were not already available, culturally appropriate translations were developed by experienced translators using both forward and backward translation.

Statistical Analysis

As previously described,10 the preplanned efficacy analysis for the MERLIN-TIMI 36 trial used a hierarchical, sequential analytic approach designed to allow for multiple comparisons while preserving overall Type I error. Because the primary study end point was nonsignificant, however, all other analyses (including the QOL analyses that form the basis of this report) are considered exploratory.

### Table 1. Baseline Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ranolazine (n=3279)</th>
<th>Placebo (n=3281)</th>
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<tbody>
<tr>
<td>Age, median (IQR), y</td>
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<td>64 (56–72)</td>
</tr>
<tr>
<td>Age ≥75 y, %</td>
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<td>Female, %</td>
<td>33.7</td>
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<td>White, %</td>
<td>94.9</td>
<td>95.4</td>
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<tr>
<td>Diabetes, %</td>
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<td>34.0</td>
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<td>Hypertension, %</td>
<td>73.5</td>
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<td>Dyslipidemia, %</td>
<td>67.2</td>
<td>67.8</td>
</tr>
<tr>
<td>Current smoker, %</td>
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<tr>
<td>Prior MI, %</td>
<td>34.5</td>
<td>33.7</td>
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<tr>
<td>Prior revascularization,* %</td>
<td>27.2</td>
<td>26.0</td>
</tr>
<tr>
<td>Prior heart failure, %</td>
<td>16.4</td>
<td>17.0</td>
</tr>
<tr>
<td>Prior angina, %</td>
<td>54.6</td>
<td>54.1</td>
</tr>
<tr>
<td>TIMI risk score, %</td>
<td></td>
<td></td>
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<tr>
<td>0–2</td>
<td>47.0</td>
<td>46.5</td>
</tr>
<tr>
<td>3–4</td>
<td>52.7</td>
<td>52.7</td>
</tr>
<tr>
<td>5–7</td>
<td>20.4</td>
<td>20.3</td>
</tr>
<tr>
<td>Early invasive strategy,%</td>
<td>40.7</td>
<td>40.7</td>
</tr>
</tbody>
</table>

*P>0.05 for all comparisons except gender (P=0.043). IQR indicates interquartile range.

**Table 1. Baseline Demographic and Clinical Characteristics**

- **Age**: median (IQR), y
- **Age ≥75 y, %**: 17.1 vs 18.0
- **Female, %**: 33.7 vs 36.1
- **White, %**: 94.9 vs 95.4
- **Diabetes, %**: 33.7 vs 34.0
- **Hypertension, %**: 73.5 vs 73.9
- **Dyslipidemia, %**: 67.2 vs 67.8
- **Current smoker, %**: 26.6 vs 24.5
- **Prior MI, %**: 34.5 vs 33.7
- **Prior revascularization, %**: 27.2 vs 26.0
- **Prior heart failure, %**: 16.4 vs 17.0
- **Prior angina, %**: 54.6 vs 54.1
- **TIMI risk score, %**: 0–2 (47.0 vs 46.5), 3–4 (52.7 vs 52.7), 5–7 (20.4 vs 20.3), Early invasive strategy (%) 40.7 vs 40.7

**Table 1. Baseline Demographic and Clinical Characteristics**

- **Age**: median (IQR), y
- **Age ≥75 y, %**: 17.1 vs 18.0
- **Female, %**: 33.7 vs 36.1
- **White, %**: 94.9 vs 95.4
- **Diabetes, %**: 33.7 vs 34.0
- **Hypertension, %**: 73.5 vs 73.9
- **Dyslipidemia, %**: 67.2 vs 67.8
- **Current smoker, %**: 26.6 vs 24.5
- **Prior MI, %**: 34.5 vs 33.7
- **Prior revascularization, %**: 27.2 vs 26.0
- **Prior heart failure, %**: 16.4 vs 17.0
- **Prior angina, %**: 54.6 vs 54.1
- **TIMI risk score, %**: 0–2 (47.0 vs 46.5), 3–4 (52.7 vs 52.7), 5–7 (20.4 vs 20.3), Early invasive strategy (%) 40.7 vs 40.7

**Table 1. Baseline Demographic and Clinical Characteristics**

- **Age**: median (IQR), y
- **Age ≥75 y, %**: 17.1 vs 18.0
- **Female, %**: 33.7 vs 36.1
- **White, %**: 94.9 vs 95.4
- **Diabetes, %**: 33.7 vs 34.0
- **Hypertension, %**: 73.5 vs 73.9
- **Dyslipidemia, %**: 67.2 vs 67.8
- **Current smoker, %**: 26.6 vs 24.5
- **Prior MI, %**: 34.5 vs 33.7
- **Prior revascularization, %**: 27.2 vs 26.0
- **Prior heart failure, %**: 16.4 vs 17.0
- **Prior angina, %**: 54.6 vs 54.1
- **TIMI risk score, %**: 0–2 (47.0 vs 46.5), 3–4 (52.7 vs 52.7), 5–7 (20.4 vs 20.3), Early invasive strategy (%) 40.7 vs 40.7
Table 2. Baseline Demographic and Clinical Characteristics, Stratified by History of Prior Angina

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>History of Prior Angina (n=3565)</th>
<th>No History of Prior Angina (n=2995)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>66 (57–73)</td>
<td>62 (54–71)</td>
</tr>
<tr>
<td>Age ≥75 y, %</td>
<td>53.1</td>
<td>43.9</td>
</tr>
<tr>
<td>Female, %</td>
<td>37.4</td>
<td>32.0</td>
</tr>
<tr>
<td>White, %</td>
<td>95.0</td>
<td>95.3</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>37.8</td>
<td>29.1</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>82.2</td>
<td>62.6</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>67.6</td>
<td>54.8</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>21.1</td>
<td>30.9</td>
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<tr>
<td>Prior MI, %</td>
<td>43.7</td>
<td>21.9</td>
</tr>
<tr>
<td>Prior revascularization,* %</td>
<td>33.4</td>
<td>18.5</td>
</tr>
<tr>
<td>Prior heart failure, %</td>
<td>25.9</td>
<td>5.7</td>
</tr>
<tr>
<td>TIMI risk score, %</td>
<td>0–2</td>
<td>16.8</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
<td>56.3</td>
</tr>
<tr>
<td></td>
<td>5–7</td>
<td>26.9</td>
</tr>
<tr>
<td>Early invasive strategy, %</td>
<td>33.2</td>
<td>49.5</td>
</tr>
</tbody>
</table>

P<0.001 for all comparisons except race (P=0.52).
*Percutaneous coronary intervention or bypass graft surgery.

and hypothesis generating. The prespecified primary end point for the QOL analyses was the SAQ anginal frequency scale.

Baseline clinical and demographic characteristics were compared between treatment arms by Wilcoxon 2-sample tests for continuous variables and chi² tests for categorical variables. Unadjusted mean scores for disease-specific health status and QOL indicators were compared between treatment arms at each of the 4 time points by independent t-tests. For the purposes of our analysis, responses for patients who returned for a final visit during the 4-month window surrounding a planned follow-up assessment were considered to have occurred at the appropriate follow-up time point. Although it was not prespecified in the original analytic plan, subsequent analyses demonstrated significant interactions between the treatment group and a history of angina before the qualifying ACS event (of the 8 health status/QOL outcomes, 4 of the interaction terms were significant at P<0.05); thus all data were analyzed in a stratified fashion.

Table 3. Baseline CAD-Specific Health Status and Quality of Life Measures, Stratified by History of Prior Angina

<table>
<thead>
<tr>
<th></th>
<th>History of Prior Angina (n=1789)</th>
<th>Placebo (n=1776)</th>
<th>No History of Prior Angina (n=1490)</th>
<th>Placebo (n=1505)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAQ angina frequency</td>
<td>52.1±2.7</td>
<td>51.2±2.7</td>
<td>76.4±2.4</td>
<td>76.7±2.4</td>
</tr>
<tr>
<td>SAQ physical limitations</td>
<td>54.5±24.3</td>
<td>54.1±24.1</td>
<td>73.0±25.1</td>
<td>73.5±25.3</td>
</tr>
<tr>
<td>SAQ angina stability</td>
<td>30.8±8.0</td>
<td>30.6±8.0</td>
<td>39.2±7.1</td>
<td>40.2±8.9</td>
</tr>
<tr>
<td>SAQ quality of life</td>
<td>37.7±19.2</td>
<td>37.5±20.2</td>
<td>47.6±21.2</td>
<td>48.4±21.1</td>
</tr>
<tr>
<td>SAQ treatment satisfaction</td>
<td>77.5±18.5</td>
<td>77.5±18.7</td>
<td>85.9±15.8</td>
<td>86.5±16.1</td>
</tr>
<tr>
<td>SF-12 physical component</td>
<td>32.3±9.6</td>
<td>32.5±9.4</td>
<td>40.4±11.2</td>
<td>40.4±11.2</td>
</tr>
<tr>
<td>SF-12 mental component</td>
<td>44.3±11.7</td>
<td>43.6±11.6</td>
<td>48.0±11.1</td>
<td>48.4±11.1</td>
</tr>
<tr>
<td>Dypnea score</td>
<td>1.92±1.41</td>
<td>1.98±1.40</td>
<td>1.28±1.37</td>
<td>1.28±1.35</td>
</tr>
<tr>
<td>EuroQol-SD</td>
<td>0.67±0.21</td>
<td>0.67±0.22</td>
<td>0.76±0.22</td>
<td>0.76±0.22</td>
</tr>
</tbody>
</table>

All values are mean±SD.
P<0.001 for all comparisons between history of prior angina and no history of prior angina; P>0.05 for all comparisons between ranolazine and placebo.

SAQ indicates Seattle Angina Questionnaire.

The primary analysis used longitudinal random coefficient growth curve models to examine the effects of treatment with ranolazine versus placebo over time on each health status/QOL outcome. Variables included in the final models for each of the health status/QOL scores were assigned treatment, history of angina, the interaction between treatment and history of angina, time, the interaction between time and treatment, and physician’s intended management strategy. In addition, the modeling process considered quadratic effect of time, the interactions between time and 1) history of angina, and 2) physician’s intended management strategy, and the 3-way interaction between time, history of angina, and treatment; these terms were included in the model if P<0.01. Exploratory models also examined the potential effect of gender, diabetes, and an early invasive strategy on health status/QOL outcomes and on the estimated treatment effect (ie, treatment×subgroup interaction). All tested interactions were selected based on a priori hypotheses, and no other interactions were examined. Treatment comparisons were performed according to the intention-to-treat principle.

All tests of statistical significance were 2-tailed, and a probability value <0.05 was considered statistically significant. All statistical analyses were performed using SAS for Windows version 9.1 (SAS Institute, Inc, Cary, NC). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Population and Baseline Health Status

Baseline characteristics of the study population are displayed in Table 1. The treatment arms were generally well matched at baseline, although there were fewer females in the ranolazine arm than in the placebo arm (34% versus 36%; P=0.043). Comparing the patients with a history of prior angina at baseline (n=3565) to those with no history of prior angina (n=2995), several clinical differences were apparent (Table 2). Those with a history of angina were more likely to be older, female, and current smokers (all P<0.001). They were more likely to have a history of diabetes mellitus, dyslipidemia, hypertension, prior MI, and previous revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery) (all P<0.001). They more often presented with higher TIMI risk scores (P<0.001) but were less likely to be treated with the intent of an early invasive strategy (history of angina versus no history of angina, 33% versus 50%; P<0.001). Among those with and without a
history of prior angina, there were no significant differences between treatment arms except for fewer females in the ranolazine versus placebo arm among those with a history of prior angina (36% versus 39%; \(P=0.045\); data not shown).

Baseline disease-specific health status and QOL measures are shown in Table 3. Patients with prior angina had lower scores for all SAQ domains, SF-12 physical and mental component scales, EuroQol-5D-derived utilities, and higher dyspnea scores (all \(P<0.001\)) than those without prior angina. All disease-specific health status and generic QOL indicators were similar at baseline between treatment arms both in the overall population and when stratified by history of prior angina.

**Follow-Up Health Status and QOL**

The rates of missing data were as follow: 8% at baseline, 6% at 4 months, 12% at 8 months, and 20% at 12 months. There were no significant differences in baseline demographic or clinical characteristics between those with missing QOL data and those with complete data and no differences between treatment arms. The unadjusted, mean health status, and QOL outcome measurements at baseline and each follow-up time point for the 2 treatment arms are shown in Figure 1. All health status and QOL measures showed significant improvement from baseline at each follow-up time point in both treatment arms, with the greatest changes occurring between baseline and the 4-month follow-up time point. In general, there were only small differences between treatment arms, with the greatest difference observed in SAQ angina frequency, for which treatment with ranolazine as compared to placebo resulted in significantly higher scores at 4 months (84.2 versus 82.3; \(P=0.002\)), 8 months (85.8 versus 83.5; \(P<0.001\)), and 12 months (86.4 versus 84.1; \(P=0.002\)). At 12 months, those in the ranolazine arm also had higher mean scores than those in the placebo arm for the SAQ QOL domain (70.4 versus 68.6; \(P=0.018\)) as well as SAQ treatment satisfaction (88.4 versus 87.3; \(P=0.019\)). None of the other health status or QOL measures differed significantly between the 2 treatment arms at any of the follow-up time points (Figure 1).
Longitudinal Analyses

The estimated effect of ranolazine versus placebo over time, among patients with and without angina before randomization, for each of the health status/QOL end points, at 4, 8, and 12 months, according to the longitudinal growth curve models are shown in Figure 2. The estimated differences between treatment groups at 12 months are presented in Table 4. In contrast to the preceding analyses (which compared

Figure 2. Mean effects of ranolazine vs placebo over time, stratified by history of prior angina. Mean effects are derived from a longitudinal growth curve model incorporating covariates for treatment group, time from randomization, and the interaction of these factors. P values refer to the 2-way interaction between treatment group and a history of prior angina, as determined from the full (nonstratified) model that also included history of prior angina.
treatment groups at each separate time point and did not account for repeated measurements), when all of the follow-up data were considered, there was evidence of a significant benefit of ranolazine among prior angina patients across each of the disease-specific and generic health status domains with the exception of the SAQ physical limitations scale ($P_{H11005} = 0.059$ at 12 months). The greatest benefits of ranolazine were observed in SAQ angina frequency (mean effect versus placebo at 12 months $= 3.4$ points; $P_{H11021} = 0.001$), SAQ QOL (mean effect $= 2.7$; $P_{H11002} = 0.001$) and SAQ treatment satisfaction (mean effect $= 1.5$; $P_{H11005} = 0.004$). Smaller benefits were seen in the SF-12 physical and mental component scores, dyspnea score and EuroQol-5D utilities. Although not statistically significant, there was a suggestion of increasing treatment benefit over time among the prior angina group (Figure 2). There were no significant differences in the trajectory of health status and QOL outcomes between treatment groups among those without prior angina.

In longitudinal analyses, female sex, diabetes mellitus, and lack of early revascularization therapy were independently associated with significantly worse health status and QOL scores. However, there was no evidence of a differential treatment effect (ie, treatment subgroup interaction) for any of these clinical or demographic factors.

**Antianginal Medications**

Use of specific classes of antianginal medications at each follow-up time point, stratified by treatment arm and prior angina status, is summarized in Figure 3. Among prior angina patients, treatment with ranolazine was associated with less use of calcium channel blockers at each follow-up time point. For long-acting nitrates, a similar trend was observed that only reached statistical significance at 12 months. For patients without prior angina, use of both calcium channel blockers and long-acting nitrates was low throughout the follow-up period and did not differ between treatment arms. $\beta$-blocker use was $= 75\%$ at each time point, irrespective of prior angina status or treatment arm.

### Table 4. Treatment Effect of Ranolazine vs Placebo at 12 Months

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>History of Prior Angina</th>
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<tbody>
<tr>
<td></td>
<td>Mean Treatment Effect (95% CI)*</td>
<td>P</td>
</tr>
<tr>
<td>SAQ angina frequency</td>
<td>3.43 (1.81, 5.05)</td>
<td>&lt;0.001</td>
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<tr>
<td>SAQ physical limitations</td>
<td>1.79 (−0.07, 3.64)</td>
<td>0.059</td>
</tr>
<tr>
<td>SAQ quality of life</td>
<td>2.66 (1.19, 4.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAQ treatment satisfaction</td>
<td>1.46 (0.46, 2.46)</td>
<td>0.004</td>
</tr>
<tr>
<td>SF-12 physical component</td>
<td>0.80 (0.04, 1.57)</td>
<td>0.040</td>
</tr>
<tr>
<td>SF-12 mental component</td>
<td>0.91 (0.17, 1.64)</td>
<td>0.016</td>
</tr>
<tr>
<td>Dyspnea score</td>
<td>−0.12 (−0.22, −0.03)</td>
<td>0.013</td>
</tr>
<tr>
<td>EuroQol-SD</td>
<td>0.015 (0.003, 0.026)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

SAQ indicates Seattle Angina Questionnaire.

*Mean treatment effect according to the longitudinal growth curve model (see Methods for details).

†2-way interaction between treatment assignment and history of prior angina.
Discussion
In this large-scale, multinational trial of moderate- to high-risk non–ST-elevation ACS patients, treatment with ranolazine when compared with placebo resulted in minimal differences in both angina frequency and disease-specific QOL over a 12-month follow-up period. In exploratory analyses, we found that the benefits of treatment on QOL were strongly influenced by patients’ prior angina status, however. Among patients with a history of angina before their ACS event (54% of the study cohort), there was a significant and sustained beneficial effect of ranolazine relative to placebo across the full spectrum of QOL and disease-specific health status measures—including angina frequency, perceived burden of disease, dyspnea, and overall treatment satisfaction. These benefits were apparent by the 4-month follow-up and persisted without attenuation (and in some cases even increased) over the full 12-month follow-up period. In contrast, there was no benefit on any of the QOL scales among those without a history of angina.

Comparison With Previous Studies
Previous studies on the effects of ranolazine have been limited to short-term follow-up of patients with chronic stable angina. In the Combination Assessment of Ranolazine In Stable Angina (CARISA) trial, 823 patients with chronic angina were randomized to receive either ranolazine or placebo and followed for 12 weeks with serial exercise treadmill tests. Exercise duration at 12 weeks improved by 116 seconds among ranolazine-treated patients versus 92 seconds in the placebo group (P = 0.01). Although there were modest reductions in the frequency of angina attacks and use of sublingual nitroglycerin in CARISA, neither disease-specific nor generic health status was assessed formally.

In the Efficacy of Ranolazine In Chronic Angina (ERICA) trial, 565 patients with stable angina, refractory to maximal doses of amlodipine, were randomized to ranolazine or placebo and followed for 6 weeks to assess for changes in anginal symptoms. Although ERICA patients had lower baseline SAQ scores than the MERLIN-TIMI 36 participants, the 6-week follow-up difference in SAQ angina frequency scores was 4.6 points—similar to the benefit observed among the MERLIN-TIMI 36 prior angina subgroup. In contrast to MERLIN-TIMI 36, however, there were no benefits of ranolazine on any of the other SAQ domains in the ERICA trial. The MERLIN-TIMI 36 trial thus adds to the evidence base by enrolling a large and relatively broad population of patients with established CAD and investigating a broad range of health status and QOL domains including dyspnea, disease-specific QOL and treatment satisfaction, in addition to angina frequency.

Clinical Significance
The large sample size of the MERLIN-TIMI 36 trial provided statistical power sufficient to detect small between-group differences in health status/QOL. It is therefore important to consider whether the benefits provided by ranolazine were clinically important or relevant, even among the subgroup with prior angina. This issue is particularly challenging because the health status/QOL benefits are measured on a continuous scale. For example, within the prior angina subgroup, the unadjusted mean treatment effect for the SAQ angina frequency scale over 12 months was 3.4 points. Direct inspection of the SAQ scoring algorithm reveals that a change of 10 points equals the minimum change perceptible on an individual level. Thus, it is clear that a mean population difference of 3.4 points is not representative of any individual and rather represents a heterogeneous response to treatment that is typical of most medical interventions, in which some patients derive substantial benefit while others derive little or no detectable benefit.

To help put this difference in SAQ angina frequency in perspective, it is noteworthy that a separate analysis of the MERLIN-TIMI 36 data demonstrated that a 1-level change in Canadian Cardiovascular Society classification between baseline and 4-months corresponded to a 7.5-point change in SAQ angina frequency over the same period of time (data not shown). A further point of reference can be found by comparing the level of QOL benefits observed in MERLIN-TIMI 36 with those obtained using percutaneous coronary intervention in the Clinical Outcomes Using Revascularization and Aggressive drug Evaluation (COURAGE) trial. In that study of more than 2000 patients with chronic stable angina, percutaneous coronary intervention was associated with a 3-point difference in SAQ anginal frequency scores at the 12-month follow-up—virtually identical to that observed with ranolazine in the prior angina subgroup of the MERLIN-TIMI 36 trial. Although these studies are different in many ways, the COURAGE results can nonetheless serve as a point of reference for the results of MERLIN-TIMI 36.

Given the heterogeneous response to treatment with ranolazine, even among the group of patients with a history of prior angina, these data do not support the use of ranolazine in all patients after an ACS event to prevent angina or to improve overall QOL. Nonetheless, our findings do suggest the hypothesis that ranolazine may provide some benefit to patients with persistent or recurrent angina during subsequent outpatient follow-up. Because this was a post hoc analysis, however, future prospectively designed trials are needed to test this hypothesis.

Limitations
This study has several important limitations. Although the QOL analyses were prespecified secondary analyses, given the nonsignificant difference in the primary endpoint of death, MI, or recurrent ischemia, the results presented here should be considered exploratory and hypothesis-generating. In addition, prior angina was not a prespecified subgroup for analysis, primarily because the MERLIN-TIMI 36 trial was designed to examine the effect of ranolazine on post-ACS mortality, recurrent MI, and severe recurrent ischemia with prespecified subgroup analyses appropriate for this composite endpoint. Nonetheless, we believe our results—particularly for the prior angina subgroup—are credible in light of both previous studies of ranolazine and their inherent biological plausibility. Moreover, because it has been shown that the strongest predictor of angina after an MI is angina before the ischemic event, we believe we have identified a subgroup at...
high likelihood for post-ACS angina, and thus potentially more likely to respond to the antianginal effects of ranolazine. Furthermore, given that early initiation of ranolazine was not associated with a reduction in irreversible end points, it is unlikely that ranolazine will be used clinically in the manner that was studied in the MERLIN-TIMI 36 trial. Instead, it is most likely that ranolazine will be prescribed for patients who have continued symptoms suggestive of coronary ischemia (eg, angina, dyspnea) after initial revascularization and medical stabilization. Although this treatment strategy was not examined directly in MERLIN-TIMI 36, given the enhanced benefits seen among the subgroup with prior angina, it is likely that the magnitude of observed benefits would have been even greater if the study had been restricted to those patients with persistent symptoms after their ACS event. Unfortunately, because all patients in the active arm of MERLIN-TIMI 36 were started on ranolazine at the time of their ACS event, the study design precludes further analyses that might help to identify characteristics associated with enhanced benefits of ranolazine if it were used in this manner. As in any clinical trial, the study results should be considered in light of the actual population enrolled. In particular, although the study inclusion criteria were relatively broad and involved a large number of countries, there was a high proportion of white individuals in the study, which may limit its generalizability to other racial groups. Finally, it is important to recognize that despite the double-blind nature of the study, there were significant differences in the use of other antianginal medications during the follow-up period. In particular, patients in the ranolazine arm were less likely to receive both long-acting nitrates and calcium channel blockers during follow-up, which may have mitigated the health status and QOL benefits of ranolazine to some degree.

Conclusions
Among a broad population of patients who presented with non–ST-elevation ACS, the addition of ranolazine to standard treatment including coronary revascularization resulted in minimal improvements in angina frequency and disease-specific QOL over a 12-month follow-up period. Posthoc subgroup analysis suggested that the benefits of ranolazine were significantly greater among the subgroup of patients with angina before their ACS event. In contrast, there were no significant benefits of ranolazine on angina or QOL among the subgroup of patients who did not have angina before their ACS event. Further prospectively designed trials are needed to definitively determine the impact of ranolazine on patients with persistent or recurrent angina after an ACS.

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References
2. Brorsson B, Bernstein SJ, Brook RH, Werko L. Quality of life of patients with chronic stable angina before and four years after coronary revascularization compared with a normal population. Heart. 2002;87:140–145.


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**CLINICAL PERSPECTIVE**

Ranolazine has been shown to reduce myocardial ischemia and symptom severity among selected patients with chronic angina. We evaluated the effects of ranolazine on health status and quality of life in 6560 patients with no–ST-elevation acute coronary syndromes using data from the MERLIN-TIMI 36 trial. Over 12 months, health status and quality of life scores improved significantly at all follow-up time points for both treatment arms. In the overall population, treatment with ranolazine as compared to placebo was associated with minimal improvements in angina frequency and disease-specific quality of life. Subsequent exploratory analyses suggested that the benefits of ranolazine were significantly greater among the subgroup of patients with angina before their acute coronary syndrome event (n = 3565). In contrast, there were no significant benefits of ranolazine on angina or quality of life among the subgroup of patients who did not have angina before their acute coronary syndrome event. Our findings suggest the hypothesis that ranolazine may provide some benefit to patients with persistent or recurrent angina during subsequent outpatient follow-up from an acute coronary syndrome. Because this was a posthoc analysis, however, future prospectively designed trials are needed to test this hypothesis.
Effects of Ranolazine on Disease-Specific Health Status and Quality of Life Among Patients With Acute Coronary Syndromes Results from the MERLIN-TIMI 36 Randomized Trial

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