Effects of Ranolazine on Quality of Life Among Patients With Diabetes Mellitus and Stable Angina

In the Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina (TERISA) trial, ranolazine reduced the frequency of angina episodes and use of sublingual nitroglycerin in patients with type 2 diabetes mellitus (T2DM) and stable angina, as assessed by a daily diary. Using data from the same trial, we evaluated the effect of ranolazine on a broader range of patients’ health status and quality of life.

### Table. Mean Change From Baseline in Disease-Specific Health Status and QOL Scores by Treatment Group

<table>
<thead>
<tr>
<th>Health Status/QOL</th>
<th>Baseline Score, Mean (SD)</th>
<th>LS Mean Change (95% CI)</th>
<th>Treatment Effect, Δ (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAQ angina frequency</td>
<td>46.3 (19.0)</td>
<td>16.1 (14.0 to 18.1)</td>
<td>13.3 (11.2 to 15.4)</td>
<td>2.8 (0.6 to 5.0)</td>
</tr>
<tr>
<td>SAQ physical limitation</td>
<td>57.3 (19.2)</td>
<td>4.3 (2.8 to 5.9)</td>
<td>4.0 (2.4 to 5.5)</td>
<td>0.3 (−1.4 to 2.1)</td>
</tr>
<tr>
<td>SAQ QOL</td>
<td>50.2 (19.6)</td>
<td>9.6 (7.7 to 11.5)</td>
<td>7.8 (5.9 to 9.7)</td>
<td>1.8 (−0.2 to 3.9)</td>
</tr>
<tr>
<td>SAQ treatment satisfaction</td>
<td>75.5 (15.4)</td>
<td>6.2 (4.7 to 7.6)</td>
<td>4.5 (3.0 to 6.0)</td>
<td>1.7 (0.1 to 3.3)</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>38.2 (6.8)</td>
<td>2.9 (2.3 to 3.5)</td>
<td>1.9 (1.3 to 2.5)</td>
<td>1.0 (0.3 to 1.6)</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>44.9 (10.1)</td>
<td>1.0 (0.2 to 1.8)</td>
<td>1.1 (0.3 to 1.9)</td>
<td>−0.1 (−1.0 to 0.8)</td>
</tr>
<tr>
<td>Rose Dyspnea Scale score</td>
<td>2.0 (1.2)</td>
<td>−0.28 (−0.39 to −0.17)</td>
<td>−0.18 (−0.29 to −0.07)</td>
<td>−0.11 (−0.23 to 0.01)</td>
</tr>
</tbody>
</table>

Abbreviations: LS, least squares; MCS, mental component summary; PCS, physical component summary; QOL, quality of life; SAQ, Seattle Angina Questionnaire; SF-36, Medical Outcomes Short Form-36.

### Methods

TERISA was approved by the national regulatory authority in each participating country and the institutional review board or local ethics committee for each site, and all participating patients provided written informed consent. TERISA was a randomized, double-blind, placebo-controlled trial in 104 sites in 14 countries in which patients with chronic stable angina receiving 1 to 2 antianginal medications and T2DM were randomized to placebo or ranolazine (Gilead Sciences; dosage goal, 1000 mg twice daily) for 8 weeks.

Health status was assessed at baseline and at 8 weeks with the Seattle Angina Questionnaire (SAQ), Rose Dyspnea Scale, and the Medical Outcomes Short Form-36 (SF-36) component scores. A 10-point increase in SAQ angina frequency represents a clinically important intra-individual change. Linguistically valid, country-specific instruments were used.

Scores were compared using analysis of covariance, adjusted for baseline health status and prespecified stratification covariates. We tested interactions between treatment and baseline angina; number of antianginals; geography (Russia, Ukraine, and Belarus vs other [as prespecified in the TERISA analytic plan]), age, and sex.

### Results

Overall, 917 patients were randomized: mean age of 64 years, 61% men, 99% white, and mean hemoglobin A1c level of 7.3%. Both treatment groups had high symptom burden at baseline and experienced improvements in all health status measures at follow-up (Table). Compared with placebo, ranolazine significantly improved SAQ angina frequency, treatment satisfaction, and SF-36 physical component summary scale scores. These effects did not differ for all measures across each of the prespecified subgroups (geography, baseline angina episodes, number of antianginals, sex, and age [P > .05 for all interactions]), except the SF-36 mental component, which improved more with ranolazine in other countries (mean effect, 1.8; 95% CI, 0.01 to 3.5) than in Russia, Ukraine, and Belarus (mean effect, −0.9; 95% CI, −2.0 to 0.2 [P value for interaction, .099]).

A greater percentage of patients treated with ranolazine vs placebo had at least a 10-point improvement in SAQ angina frequency scores (67% vs 58% [P = .004; Figure], suggesting that 11 patients need to be treated with ranolazine for 1 to experience a clinically significant improvement in angina. The number needed to treat was lower among patients taking more
Figure. Cumulative Response Curve of Change in Seattle Angina Questionnaire (SAQ) Angina Frequency by Treatment Group

![Cumulative Response Curve](image)

A, Entire study population; B, focuses on the most common changes from baseline to 8 weeks (86% of the study population). Cumulative response curves plotted change in SAQ angina frequency from baseline to 8 weeks on the x-axis and the percentage of patients who achieved at least that amount of change on the y-axis.

Discussion | In a multinational trial of patients with T2DM and stable angina, ranolazine modestly improved key measures of disease-specific and generic health status, with benefits generally consistent across each prespecified subgroup. Furthermore, a greater proportion of patients experienced clinically meaningful improvements in angina with ranolazine vs placebo, particularly among those with more baseline angina and taking more antianginal medications. These data complement our prior reports of reduced angina frequency using an electronic diary by revealing that, from patients’ perspectives, multiple health status domains improved more with ranolazine than with placebo.

TERISA was limited by a racially narrow patient population. Furthermore, our interaction analyses may have been underpowered, leading to potential type II error. Specifically, the interaction of geography by treatment was significant in the main TERISA study using an angina diary, but not from patients with more angina at baseline (7 vs 49 for SAQ angina frequency <50 vs ≥50).

In conclusion, ranolazine reduced angina, particularly among those with more severe angina, improved treatment satisfaction and physical functioning in patients with T2DM and chronic stable angina.

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Administrative, technical, or material support: Yue.

Study supervision: Kosiborod, Ben-Yehuda, Spertus.

Conflict of Interest Disclosures: Dr Arnold received research support from Gilead Sciences, Genentech, and sanofi-aventis. Dr Kosiborod received research support from Gilead Sciences, American Heart Association, Medtronic Minimed, Genentech, sanofi-aventis, Glumetrics, and Maquet; is a consultant for Gilead Sciences, Genentech, F Hoffmann-La Roche, Medtronic Minimed, AstraZeneca, Abbvie, and Regeneron; and served on the advisory board for Gilead Sciences. Dr McGuire is a consultant for Janssen Pharmaceuticals, Daiichi Sankyo, Pfizer, Boehringer-Ingelheim, Regeneron, Genentech, F Hoffmann-La Roche, Merck, Bristol-Myers Squibb, Tethys Biosciences, AstraZeneca, Orexigen, Eli Lilly, and Takeda. Dr Yue is an employee of and owns stock and stock options in Gilead Sciences. Dr Ben-Yehuda is a former employee of Gilead Sciences. Dr Spertus has received research support from Gilead Sciences, National Heart, Lung, and Blood Institute, American College of Cardiology, American Heart Association, Patient-Centered Outcomes Research Institute, Amgen, Genentech, and Eli Lilly; is a consultant for Gilead Sciences, Genentech, Amgen, and United Healthcare (Scientific Advisory Group); and is a board member for Health Outcomes Sciences; and holds the copyrights for the Seattle Angina Questionnaire, Kansas City Cardiomyopathy Questionnaire, and Peripheral Artery Questionnaire. No other disclosures are reported.

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Role of the Sponsor: As the present study was a planned secondary analysis of the TERISA trial, Gilead Sciences had a role in the design and conduct of the study. The data were collected by Gilead Sciences, who had a role in

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interpretation of the data and in the preparation and review of the manuscript. An independent statistical analysis of the data was conducted by the study authors. The sponsor had no role in approval of the manuscript and decision to submit the manuscript for publication.

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Trial Registration: clinicaltrials.gov Identifier: NCT01425359


Decreased Red Blood Cell Use and Mortality in Hospitalized Patients

Blood conservation strategies effectively decrease red blood cell (RBC) use in specific patient groups.1-3 However, the impact of RBC transfusion reduction on mortality in a diverse inpatient population remains poorly described. We detail the impact of declining RBC use on 30-day mortality within Kaiser Permanente Northern California (KPNC), an integrated health care delivery system serving 3.5 million members at 21 hospitals.

Methods | The KPNC and University of California, San Francisco (UCSF) institutional review boards approved this study and waived the requirement for informed consent based on the nature of the study. Beginning in 2010, KPNC initiated a regional blood conservation program whose key features included (1) clinician education in evidence-based transfusion guidelines; (2) focused multidisciplinary conservation efforts in specific high-use departments (eg, orthopedics, cardiovascular surgery); and (3) guideline-based clinical decision support embedded within the electronic medical record.

To study the impact of these initiatives, we quantified RBC transfusion in an inpatient cohort composed of all non-obstetric patients 18 years or older admitted to KPNC hospitals between July 1, 2009, and August 31, 2013. We evaluated the impact of decreased RBC use on unadjusted and risk-adjusted 30-day mortality prior to (2010) and following (2012-2013) reductions in blood use. We examined these rates in patients with hemoglobin levels below 10 g/dL (to convert to grams per liter, multiply by 10) during hospitalization (n = 218,056), accounting for nearly all (81,897 of 83,461 [98.1%]) transfused patients. We quantified patients’ predicted 30-day mortality rates based on prior methods adjusting for age, sex, comorbid disease burden, emergency or elective presentation, medical or surgical admission, admission diagnosis, severity of illness, first inpatient ward, and hospital facility.4 We also adjusted for patients’ preadmission hemoglobin level and lowest hospital hemoglobin level.5 We then compared standardized mortality ratios for transfused vs nontransfused patients using Poisson regression. Trends in RBC use and unadjusted 30-day mortality were assessed using linear regression. Statistical analyses were performed in Stata 11 software (StataCorp).

Results | The number of RBC units transfused decreased 8.6% annually from 41.8 units per 100 patients in 2010 (95% CI, 41.1-42.6 units) to 31.0 units per 100 patients in 2013 (95% CI, 30.3-31.8 units) (P < .001) (Figure 1). From 2009 to 2013, the...