Evaluation of the Glycometabolic Effects of Ranolazine in Patients With and Without Diabetes Mellitus in the MERLIN-TIMI 36 Randomized Controlled Trial

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Background—Ranolazine is a novel antianginal shown in an exploratory analysis in patients with diabetes mellitus and chronic angina to be associated with a decline in hemoglobin A1c (HbA1c). We designed a prospective evaluation of the effect of ranolazine on hyperglycemia as part of a randomized, double-blind, placebo-controlled outcomes trial.

Methods and Results—We compared HbA1c (percentage) and the time to onset of a ≥1% increase in HbA1c among 4918 patients with acute coronary syndrome randomized to ranolazine or placebo in the MERLIN-TIMI 36 trial. Ranolazine significantly reduced HbA1c at 4 months compared with placebo (5.9% versus 6.2%; change from baseline, −0.30 versus −0.04; P < 0.001). In patients with diabetes mellitus treated with ranolazine, HbA1c declined from 7.5 to 6.9 (change from baseline, −0.64; P < 0.001). Diabetic patients were more likely to achieve an HbA1c <7% at 4 months with ranolazine compared with placebo (59% versus 49%; P < 0.001) and were less likely to have a ≥1% increase in HbA1c (14.2% versus 20.6% at 1 year; hazard ratio, 0.63; 95% confidence interval, 0.51 to 0.77; P < 0.001). Moreover, ranolazine reduced recurrent ischemia in diabetic patients (hazard ratio, 0.75; 95% confidence interval, 0.61 to 0.93; P = 0.008). Notably, in patients without diabetes mellitus at baseline, the incidence of new fasting glucose >110 mg/dl or HbA1c ≥6% was reduced by ranolazine (31.8% versus 41.2%; hazard ratio, 0.68; 95% confidence interval, 0.53 to 0.88; P = 0.003). Reported hypoglycemia did not increase with ranolazine (P = NS).

Conclusions—Ranolazine significantly improved HbA1c and recurrent ischemia in patients with diabetes mellitus and reduced the incidence of increased HbA1c in those without evidence of previous hyperglycemia. The mechanism of this effect is under investigation. (Circulation. 2009;119:2032-2039.)

Key Words: angina ▪ coronary disease ▪ diabetes mellitus ▪ hemoglobin A1c

Diabetes mellitus (DM) is a global health challenge marked by a steady rise in worldwide prevalence1 and substantial associated cardiovascular morbidity and mortality.2 On the basis of data from the Centers for Disease Control Diabetes Surveillance System, it has been estimated that ≈30% of individuals with DM 35 to 64 years of age have cardiovascular disease and that this proportion is as high as 45% among DM patients 65 to 74 years of age.1 Nearly 3 million Americans have been diagnosed with DM and coronary artery disease, and the incidence of DM appears to be increased in patients with acute coronary syndrome, who often manifest abnormal glucose metabolism at presentation.3,4 The presence of DM is associated with poorer outcomes in patients with stable and unstable coronary artery disease.2,5 Moreover, the number of individuals whose prognosis is impaired in association with dysglycemia is substantially larger when those with impaired glucose metabolism, a progenitor of DM, are considered.6 Aimed at preventing microangiopathy, neuropathy, and possibly macrovascular disease, treatment of hyperglycemia is a key goal of secondary preventive therapy, with a target of reducing hemoglobin A1c (HbA1c) to ≤7%, in patients with atherosclerosis.7-9

Received January 4, 2008; accepted January 30, 2009.

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Guest Editor for this article was Roberto Bolli, MD.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.763912/DC1.


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Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIRCULATIONAHA.107.763912

2032
Ranolazine, a novel oral antianginal agent, became available in the United States in 2006 for the treatment of selected patients with chronic angina. It improves exercise performance and reduces the frequency of angina in patients with stable angina. Intriguingly, in an exploratory analysis from a trial in patients with chronic angina, ranolazine was found to be associated with a significant reduction in HbA1c. We recently reported the primary results of the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial, which showed that ranolazine reduced recurrent ischemia in a substantially broader population than previously studied and that its electrophysiological effects were associated with a significant reduction rather than an increase in arrhythmias. As part of the trial design, we prospectively planned to evaluate the effect of ranolazine on HbA1c and clinical outcomes among patients with DM in this multinational, randomized, placebo-controlled trial.

Methods

Patient Population

The study design, investigators, and primary results of the MERLIN-TIMI 36 trial have been published previously. Between 2004 and 2006, 6560 patients with non–ST-elevation acute coronary syndrome with at least 1 indicator of moderate to high risk of recurrent ischemic events underwent randomization at 440 sites in 17 countries. Major exclusion criteria included cardiogenic shock, clinically significant hepatic disease, end-stage renal disease, treatment with agents known to prolong the QT interval, or a life expectancy of <12 months. The protocol was approved by the relevant institutional review boards at all participating centers. Written informed consent was obtained from all patients.

Study Procedures

Eligible patients were randomly assigned in a 1:1 ratio to receive either ranolazine or placebo initiated as an intravenous infusion and followed by oral administration at a dose of 1000 mg twice daily until the end of the study, except in cases of a protocol-specified reduction in dose (eg, for patients with new renal insufficiency or persistent prolongation of the QT interval). Randomization was stratified according to the responsible physician’s intended management strategy (early invasive versus conservative), declared at the time of randomization. Patients returned for study visits at 14 days and 4 months and every 4 months thereafter until the end of the study visit for each subject. All available data were included in the analyses except for a single imausible value of 41.6%. HbA1c values were not available predominantly because the patient declined, because the patient withdrew from the main study, or for logistical reasons in 984 patients at baseline, 1692 at 4 months, 1247 at 8 months, and 1082 at the final visit.

End Points

An end point of worsening hyperglycemia was defined as a ≥1% increase in HbA1c. In the absence of a history of DM at enrollment, new DM was defined by any of the following: fasting plasma glucose ≥126 mg/dL at ≥14 days after enrollment, plasma glucose ≥200 mg/dL at 2 hours after the glucose load during an oral glucose tolerance test, or new DM reported by the investigator. New hyperglycemia in those with no laboratory evidence of prior dysglycemia was defined as fasting glucose ≥110 mg/dL or HbA1c ≥6% in those patients with fasting glucose <100 mg/dL and HbA1c <6% at baseline. Oral glucose tolerance test data at 0 and 2 hours were available for 3195 patients. Each of these diabetes-related end points was defined in a statistical analysis plan that was finalized before locking of the database and examination of the data. An exploratory analysis based on the cut point from professional guidelines for patients with DM was performed to determine the proportion of patients with DM and HbA1c <7% at each visit.

The major cardiovascular efficacy and safety end points have been described in detail. The primary efficacy end point of the trial was the first occurrence of any element of the composite of cardiovascular death, myocardial infarction, or recurrent ischemia. Given the established indication for ranolazine as an antianginal agent, we also separately evaluated the incidence of recurrent ischemia and the composite end point of cardiovascular death or myocardial infarction. The average duration of follow-up was 348 days.

Statistical Analyses and End Points

Baseline clinical characteristics are reported using the median and 25th and 75th percentiles for continuous variables and proportions for categorical characteristics. HbA1c and glucose data are reported as least-squares mean estimates. Analyses of HbA1c and other laboratory measurements and safety assessments were conducted using the actual treatment received (a single dose or more). All cardiovascular efficacy analyses were conducted according to the intention-to-treat principle. HbA1c and glucose values were compared between treatment groups using a generalized linear mixed effects model (SAS PROC GENMOD), assuming an exchangeable working correlation matrix, with effects for treatment, intention for early invasive management, time, and the interaction term for treatment by time. Interactions with baseline glycemic status were tested with the addition of interaction terms. Simple Pearson correlation coefficients also were calculated.

Time-to-event analyses were performed using the log-rank test stratifying by the intention to use an early invasive strategy. Hazard ratios (HRs) and 95% confidence limits were estimated with a Cox proportional-hazards model (SAS PHREG) with effects for treatment and stratified by intention for early invasive strategy. Event rates, including the cumulative incidence of worsening hyperglycemia, are presented as Kaplan–Meier failure rates at 12 months. Exploratory analyses were conducted among the subgroups of patients with and without metabolic syndrome, including those with evidence of hyperglycemia but without prior diagnosis of diabetes, given prior evidence for the higher likelihood of progression of dysglycemia in these groups.

The investigators had full access to the data. The raw database was provided to the TIMI Study Group, and all analyses reported here were carried out independently by the TIMI Study Group; study group members wrote this report and take full responsibility for the data. All authors have read and agree to the manuscript as written.
Analyses were conducted with STATA SE 9.2 (Stata Corp, College Station, Tex) and SAS 9.1 (SAS Institute, Inc, Cary, NC).

Results

Of the 6560 patients enrolled in the MERLIN-TIMI 36 trial, 2220 (33.8%) had a history of DM. Evaluation of HbA1c at enrollment (n=5576) in those with (n=1950) and without (n=3626) a history of DM revealed a substantially higher proportion of patients (49%) with evidence of chronic hyperglycemia (HbA1c ≥6.0 to <6.5%, 898 [16%]; HbA1c ≥6.5 to <7.0%, 497 [9%]; HbA1c ≥7.0%, 1343 [24%]). Among patients without previously diagnosed DM, 466 (13%) had a baseline HbA1c ≥6.5%. In addition, 271 (6%) of patients without recognized DM had a baseline fasting glucose ≥126 mg/dL or casual glucose ≥200 mg/dL.

Among patients with DM with available diabetes treatment data (n=2028), a total of 578 (29%) were treated with insulin with or without oral agents, 1127 (56%) with oral agents without insulin, and 253 (12%) with dietary intervention alone; 70 patients (3%) were reported as receiving no treatment. Among patients treated with oral agents, 404 (36%) were managed with ≥2 agents before hospitalization for the qualifying event.

Effect of Ranolazine on HbA1c

All Patients

Serial determinations of HbA1c at baseline and any subsequent time point were available for 4918 patients. Baseline characteristics were well balanced among those in this subgroup randomized to ranolazine compared with placebo (the Table). Their clinical characteristics were qualitatively similar to those without HbA1c data (Table in the online-only Data Supplement). At baseline, the concentration of HbA1c was 6.2% in both groups, and the use of insulin and oral hypoglycemic agents was well balanced (the Table). In the overall population, HbA1c (±SEM) was significantly lower at 4 months in patients treated with ranolazine (5.9±0.03%) compared with placebo (6.2±0.03%); absolute change from baseline was −0.30±0.03% with ranolazine compared with −0.04±0.03% with placebo (P<0.001).

### Table. Baseline Characteristics of the Cohort With Serial HbA1cAll Subjects Diabetes Mellitus No Diabetes Mellitus

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ranolazine (n=2441)</th>
<th>Placebo (n=2477)</th>
<th>Ranolazine (n=1401)</th>
<th>Placebo (n=1428)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (25th–75th percentiles), y</strong></td>
<td>63 (55–71)</td>
<td>64 (55–71)</td>
<td>64 (57–71)</td>
<td>65 (57–72)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>33.3</td>
<td>36.2</td>
<td>39.6</td>
<td>43.2</td>
</tr>
<tr>
<td>Weight, median (25th–75th percentiles), kg</td>
<td>81 (72–92)</td>
<td>81 (72–91)</td>
<td>85 (75–96)</td>
<td>84 (74–95)</td>
</tr>
<tr>
<td>Body mass index, median (25th–75th percentiles), kg/m²</td>
<td>28 (26–31)</td>
<td>28 (26–32)</td>
<td>30 (27–33)</td>
<td>30 (27–33)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>33.1</td>
<td>35.3</td>
<td>·</td>
<td>·</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>73.6</td>
<td>74.3</td>
<td>84.4</td>
<td>84.5</td>
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<td>Hyperlipidemia, %</td>
<td>67.1</td>
<td>68.2</td>
<td>73.8</td>
<td>75.9</td>
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<tr>
<td>Current smoker, %</td>
<td>26.4</td>
<td>25.2</td>
<td>19.5</td>
<td>17.4</td>
</tr>
<tr>
<td>Prior myocardial infarction, %</td>
<td>34.8</td>
<td>33.7</td>
<td>36.8</td>
<td>36.4</td>
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<tr>
<td>Prior heart failure, %</td>
<td>17.3</td>
<td>18.6</td>
<td>21.4</td>
<td>20.8</td>
</tr>
<tr>
<td>Estimated* creatinine clearance &lt;60 mL/min, %</td>
<td>19.6</td>
<td>20.5</td>
<td>20.7</td>
<td>20.9</td>
</tr>
<tr>
<td>Index event, %</td>
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<td>47.8</td>
<td>56.3</td>
<td>54.8</td>
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<tr>
<td>Non-ST-elevation MI</td>
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<td>49.7</td>
<td>42.3</td>
<td>43.0</td>
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<tr>
<td>Other</td>
<td>1.8</td>
<td>2.5</td>
<td>1.4</td>
<td>2.2</td>
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<td>ST-segment depression ≥0.1 mV, %</td>
<td>34.0</td>
<td>35.3</td>
<td>27.7</td>
<td>33.8</td>
</tr>
<tr>
<td>TIMI risk score, %</td>
<td>27.3</td>
<td>27.2</td>
<td>22.9</td>
<td>20.1</td>
</tr>
<tr>
<td>0–2</td>
<td>52.8</td>
<td>53.0</td>
<td>50.5</td>
<td>51.4</td>
</tr>
<tr>
<td>3–4</td>
<td>19.9</td>
<td>19.8</td>
<td>26.6</td>
<td>28.4</td>
</tr>
<tr>
<td>Time from onset of pain to randomization, median (25th–75th percentiles), n</td>
<td>24 (13–34)</td>
<td>23 (13–34)</td>
<td>23 (13–33)</td>
<td>24 (14–36)</td>
</tr>
<tr>
<td>Treatment before randomization, %</td>
<td>8.1</td>
<td>9.3</td>
<td>25.3</td>
<td>26.1</td>
</tr>
<tr>
<td>Insulin</td>
<td>20.3</td>
<td>21.3</td>
<td>61.5</td>
<td>60.6</td>
</tr>
<tr>
<td>Oral hypoglycemic agent</td>
<td>6.20±0.04</td>
<td>6.22±0.04</td>
<td>7.53±0.06</td>
<td>7.45±0.06</td>
</tr>
<tr>
<td>HbA1c (mean±SEM), %</td>
<td>116 (88–146)</td>
<td>116 (88–147)</td>
<td>107 (80–139)</td>
<td>108 (81–140)</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, median (25th–75th percentiles), mg/dL</td>
<td>43 (35–51)</td>
<td>43 (35–51)</td>
<td>40 (34–48)</td>
<td>41 (34–49)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, median (25th–75th percentiles), mg/dL</td>
<td>35 (28–42)</td>
<td>35 (28–42)</td>
<td>35 (28–42)</td>
<td>35 (28–42)</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction.

*Estimated with the Cockcroft-Gault equation.
Patients With Previously Diagnosed DM
Among patients previously diagnosed with DM, by 4 months, HbA1c declined by an absolute 0.64% (7.5% to 6.9%; Figure 1) in patients treated with ranolazine compared with a 0.22% decline (7.4% to 7.2%) in those treated with placebo (P<0.001 for ranolazine versus placebo). As such, patients with DM were significantly more likely to achieve an HbA1c ≤7% at 4 months when treated with ranolazine compared with placebo (466 [59%] versus 409 [49%]; P<0.001). The significant effect of ranolazine on HbA1c at 4 months emerged despite the similar use of ≥2 hypoglycemic agents in the ranolazine and placebo groups at 4 months (124 [17.5%] versus 145 [18.8%]; P=0.52). Moreover, the incidence of an increase in HbA1c by ≥1% during follow-up was significantly reduced in diabetic patients treated with ranolazine compared with placebo (14.2% versus 20.6% at 1 year; HR, 0.63; 95% confidence interval [CI], 0.51 to 0.77; P<0.001). Thus, patients allocated to ranolazine remained more likely to achieve an HbA1c ≤7% at 8 months (335 [56%] versus 317 [48%]; P=0.006) and at the final visit (454 [58%] versus 416 [50%]; P=0.002).

Patients Without Previously Diagnosed DM
Notably, an effect of ranolazine on HbA1c was also apparent in those patients without a history of DM. By 4 months, a statistically significant, albeit small, decline in HbA1c was found in patients allocated to ranolazine (change from baseline, −0.12±0.03; P<0.001) compared with a rise in HbA1c in patients without a history of DM allocated to placebo.
(change from baseline, 0.06±0.02; P=0.02), resulting in a significant difference between treatment groups (P<0.001; Figure 1). The effect of ranolazine on HbA1c, although statistically significant, was smaller in those without compared with those with DM (P for interaction<0.001). No apparent influence was found from the presence of the metabolic syndrome among those without DM on the change in HbA1c in the ranolazine group (metabolic syndrome: n=630; change, −0.11±0.04; P=0.01; without metabolic syndrome: n=771; change, −0.14±0.03; P<0.001). However, this effect of ranolazine was larger (change, −0.82±0.12 with ranolazine versus −0.36±0.12 with placebo; P=0.002) in patients without a history of DM but with evidence of hyperglycemia at enrollment (n=357 with HbA1c ≥7.0%, fasting glucose >126 mg/dL, or casual glucose ≥200 mg/dL) compared with those not meeting these parameters (P for interaction=0.01). Interestingly, in patients with normal glucose indexes at enrollment (n=664 with fasting glucose <100 mg/dL and HbA1c <6%), the probability of developing a new fasting glucose ≥110 mg/dL, or HbA1c ≥6% was also significantly reduced by ranolazine (31.8% versus 41.2% at 1 year; HR, 0.68; 95% CI, 0.53 to 0.88; P=0.003). New-onset DM was not significantly reduced by ranolazine (10.8% versus 11.5% at 1 year; HR, 0.91; 95% CI, 0.76 to 1.08; P=0.28).

Other Glycemic Parameters

Examination of the change in plasma glucose in all patients with available samples (Figure 2) revealed a nonsignificant trend toward a greater decline in glucose in patients allocated to ranolazine compared with placebo among patients with DM (n=1670) and no difference in those without DM (n=3439). Among patients with DM, serial fasting and nonfasting glucose measurements were available for 779 and 580 patients, respectively. No difference in fasting glucose values were found between the 2 treatment groups (P=0.32 at each time point). A pattern of lower nonfasting glucose values with ranolazine was found that was not statistically significant (4 months: 172±4.7 versus 177±4.3 mg/dL, P=0.43; 8 months: 162±4.5 versus 172±4.4 mg/dL, P=0.085). An exploratory assessment of the relationship between the change in nonfasting plasma glucose and HbA1c in the 2 treatment groups revealed a stronger association among patients treated with ranolazine (r=0.38) compared with placebo (r=0.13, P for interaction<0.001). No significant difference in this relationship was found when fasting glucose values were examined (r=0.25 for ranolazine, r=0.27 for placebo, P for interaction=0.27).

No clinically meaningful difference in lipid profile was found in patients with DM treated with ranolazine compared with placebo. In addition, ranolazine was not associated with any significant change in body weight from baseline to the end of the study in patients with DM (estimated mean±SE, −0.06±0.20 kg in the ranolazine group versus 0.35±0.20 kg in the placebo group; P=0.14) and without DM (estimated mean±SE, 0.17±0.15 versus 0.31±0.18 kg, respectively; P=0.52). Reported hypoglycemia in patients with DM was similar between treatment groups (29 with ranolazine [2.6%] versus 28 with placebo [2.5%]).

Clinical Efficacy and Safety of Ranolazine as an Antianginal Agent in Patients With DM

Consistent with the results in the overall cohort (HR, 0.87; 95% CI, 0.76 to 0.99), treatment with ranolazine in patients with DM resulted in a significant reduction in recurrent ischemia (HR, 0.75; 95% CI, 0.61 to 0.93; P=0.008; Figure 3) with borderline statistical evidence of heterogeneity compared with patients without DM (HR, 0.95; 95% CI, 0.80 to 1.11; P for interaction=0.10) and did not affect the risk of cardiovascular death or myocardial infarction (HR, 1.09; 95% CI, 0.86 to 1.38; P=0.46; P for interaction=0.29).

Among patients with DM treated with ranolazine, no excess of death resulting from any cause (HR, 0.98; 95% CI, 0.70 to 1.36; P=0.89; P for interaction=0.91) or sudden cardiac death (HR, 0.76; 95% CI, 0.41 to 1.39; P=0.37) was found compared with those treated with placebo. The incidence of new or worsening heart failure also did not differ with ranolazine versus placebo (HR, 1.10; 95% CI, 0.73 to 1.39; P=0.95; P for interaction=0.68). As in the overall cohort, the incidence of ventricular tachycardia (≥8 beats) observed during Holter monitoring in patients with DM
(n=2152) was lower in the ranolazine group (4.7%) compared with the placebo group (6.8%; P=0.037).

Discussion
The results of this prospectively planned analysis from a large, randomized, double-blind, placebo-controlled trial establish that the novel antianginal agent ranolazine reduces HbA1c in patients with DM and may mitigate new hyperglycemia in patients at risk for DM. At the same time, we provide evidence for the consistent antianginal effects and the cardiovascular and overall safety of ranolazine among patients with DM and high-risk coronary artery disease. Together, these 2 findings point toward ranolazine as an attractive antianginal agent for patients with chronic angina and impaired glucose metabolism.

Effects of Ranolazine on Hyperglycemia
Ranolazine has been shown to exert its anti-ischemic and antianginal actions without effects on heart rate or blood pressure. Initial evidence supporting ranolazine as a metabolic modulator sparked interest in its potential for favorably influencing hyperglycemia. In an exploratory analysis among 131 patients with chronic angina, DM, and serial determinations of HbA1c in the Combination Assessment of Ranolazine in Stable Angina (CARISA) trial, ranolazine was shown to be associated with statistically significant 0.50% and 0.72% absolute declines in HbA1c by 12 weeks with dosing of 750 and 1000 mg BID, respectively, compared with a −0.02% change in the placebo group.13 Our prospective analysis in the much larger population with serial HbA1c from MERLIN-TIMI 36 demonstrates a 0.64% decline in HbA1c at 16 weeks in patients with DM receiving ranolazine compared with 0.24% in those receiving placebo. Moreover, in the present study, the significant reduction in HbA1c with ranolazine was observed despite a relatively low mean HbA1c in patients with DM at baseline (7.5%) and the unrestricted clinical management of hyperglycemia in both of the blinded treatment groups. Long-term comparable changes in HbA1c were associated with a decrease in the incidence of cardiovascular complications of DM. It is not surprising, given the relatively short duration of follow-up, that any impact of improved HbA1c with ranolazine on macrovascular events was not seen in this study.

Despite these intriguing findings with respect to the influence of ranolazine on the concentration of HbA1c, additional studies are needed to establish the pathobiological mechanisms underlying this consistent epidemiological observation. On the basis of findings from experimental models, the mechanism of action of ranolazine as an antianginal agent was initially proposed to be through partial inhibition of fatty acid oxidation, resulting in a shift of cellular metabolism toward the more oxygen-efficient use of glucose. However, subsequent research has demonstrated this effect on substrate use to occur only at concentrations substantially higher than those at which ranolazine is observed to have its clinical effect on angina. Concurrently, at concentrations similar to that achieved with its clinically approved dosing (500 to 1000 mg twice daily), ranolazine has been shown inhibit the slowly inactivating component of the cardiac sodium current (late I\textsubscript{Na}). By preventing cellular sodium and calcium overload, ranolazine reduces myocyte dysfunction and may reduce myocardial wall stress, oxygen consumptions, and microvascular compression, thereby favorably altering the balance between myocardial oxygen supply and demand.

These actions of ranolazine do not offer an immediate explanation for its effect on HbA1c. However, preliminary findings from experimental models demonstrated that ranolazine increased glucose-stimulated insulin secretion in isolated pancreatic islets and in awake rats after an intravenous glucose load. This observation points to a possible role for ion channels on pancreatic β cells in the secretion of insulin. Whether these findings are due to the effects on sodium channels and indirectly on intracellular adenosine triphosphate and calcium remains to be determined. The theoretical possibilities that ranolazine may shorten erythrocyte lifespan or inhibit glucuronidation of hemoglobin, thereby influencing HbA1c without altering glycemic control, may be considered unlikely because no effect of ranolazine on hematocrit was found, and the only potential adduct of ranolazine (2,6-dimethyl aniline) that could plausibly interfere with glucuronidation of hemoglobin is not a metabolite of ranolazine in humans. In addition, exploratory analyses in this study indicated that ranolazine significantly strengthened the relationship between change in nonfasting glucose and change in HbA1c, lending some support to the hypothesis from preclinical findings that ranolazine may reduce HbA1c through increased glucose-stimulated insulin secretion. Nevertheless, additional investigations of the mechanism underlying our observations are needed to corroborate a clinically meaningful effect of ranolazine on glucose homeostasis in humans.

Study Limitations
Because this study, albeit prospectively designed, was ancillary to the main objectives for MERLIN-TIMI 36, data for HbA1c and glucose could not be obtained for all subjects, and diabetes status at enrollment was based on patient history. Moreover, the timing and conditions of glucose measurement were not controlled. Thus, missing data may adversely affect the generalizability of our findings. Nevertheless, because the reasons for missing data are expected to be largely random in nature, any impact on the qualitative conclusions may reasonably be anticipated to be small. In addition, the lack of controlled timing of glucose measurements may have contributed to the lack of a significant difference in glucose measurements in our study. Because testing for HbA1c was performed with locally available assays, the absolute change in HbA1c observed reflects the distribution of assays used and cannot be referenced to a single reference assay. For these reasons, additional studies designed specifically to assess the glycometabolic effects of ranolazine are needed to corroborate the clinical applicability of our findings.

Potential Clinical Implications
If supported by ongoing mechanistic studies and additional studies designed with a focus on glycometabolic effects, the finding of a significant favorable effect of ranolazine on glycemia could be of clinical importance. The overlapping presentation of coronary artery disease and DM is common-
place and is increasing with the prevalence of obesity worldwide. Although achieving an HbA1c concentration <7% is established as a guideline for secondary prevention among patients with established coronary artery disease,\textsuperscript{7} data from the National Health and Nutrition Examination Survey indicate that <50% of patients with DM achieve this goal.\textsuperscript{21} Therefore, there continues to be a strong interest in new agents to manage hyperglycemia in this patient population.\textsuperscript{22}

In addition, the cardiovascular safety of some oral hypoglycemic agents has been challenged, with experts pointing to a need for adequately powered clinical outcomes trials.\textsuperscript{23–25} Moreover, the adverse glycometabolic effects of β1-selective β-blockers are a consideration in patients with DM. Thus, an effective antianginal agent with established cardiovascular and overall safety in a large outcomes trial that increases the proportion of patients meeting current goals for management of hyperglycemia would have particular appeal for the treatment of angina in this high-risk population.

**Conclusions**

Ranolazine significantly lowered HbA1c in patients with established coronary artery disease and DM and reduced the incidence of increased HbA1c in those without evidence of previous hyperglycemia. The mechanism of this effect is under investigation.

**Source of Funding**

The MERLIN-TIMI 36 trial was supported by CV Therapeutics Inc.

**Disclosures**

The TIMI Study Group has received significant research grant support from Accentumics, Amgen, Astra-Zeneca, Bayer Healthcare, Beckman Coulter, Biosite, Bristol-Myers Squibb, CV Therapeutics, Eli Lilly and Co, GlaxoSmithKline, Inotek Pharmaceuticals, Integrated Therapies, Merck and Co, Merck-Schering Plough Joint Venture, Millennium Pharmaceuticals, Novartis Pharmaceuticals, Nuvelo, Ortho-Clinical Diagnostics, Pfizer, Roche Diagnostics, Sanofi-Aventis, Sanofi-Synthelabo, and Schering-Plough. Dr Morrow has received honoraria for educational presentations from CV Therapeutics and Sanofi-Aventis. He has served as a consultant for GlaxoSmithKline and Sanofi-Aventis and on an advisory board for Genentech. Dr Scirica has received honoraria for educational presentations from CV Therapeutics. Dr Chaitman has received research grant support and honoraria for educational presentations from CV Therapeutics. Dr Karwatowska-Prokopczuk is an employee of and owns stock in CV Therapeutics. Dr McGuire has received research grant support from GlaxoSmithKline, served on the speaker’s bureaus for Takeda and Pfizer, and served as a consultant for CV Therapeutics, Johnson & Johnson, and Sanofi-Aventis. Dr Braunwald has received honoraria for educational presentations and consulting from CV Therapeutics. The other authors report no conflicts.

**References**


Ranolazine is a novel antianginal that may also have a favorable effect on hemoglobin A1c (HbA1c). We designed a prospective evaluation of the effect of ranolazine on hyperglycemia as part of the randomized, double-blind, placebo-controlled Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial and compared HbA1c (percentage) among 4918 patients with acute coronary syndrome randomized to ranolazine or placebo. We found that ranolazine significantly reduced HbA1c at 4 months compared with placebo in patients with and without diabetes mellitus. In patients with diabetes mellitus treated with ranolazine, HbA1c declined 0.64% ($P<0.001$). In addition, diabetic patients treated with ranolazine were more likely to achieve an HbA1c $\leq 7\%$ at 4 months ($P<0.001$). Notably, in patients without diabetes mellitus at baseline, the incidence of new fasting glucose $>110$ mg/dL or HbA1c $\geq 6\%$ was reduced by 32% with ranolazine ($P=0.003$). If supported by mechanistic studies, the finding of a significant favorable effect of ranolazine on glycemia is likely to be clinically important. The overlapping presentation of coronary artery disease and diabetes mellitus is commonplace and is increasing worldwide. The goal of achieving an HbA1c concentration $<7\%$ is established as a guideline for secondary prevention among patients with coronary artery disease but is often not met. Moreover, the cardiovascular safety of some oral hypoglycemic agents has been challenged, with experts pointing to a need for large safety trials. Thus, an effective antianginal that enhances the management of hyperglycemia, with established cardiovascular safety in a large outcomes trial, would be of particular appeal for the treatment of angina in the high-risk population with diabetes mellitus.
Evaluation of the Glycometabolic Effects of Ranolazine in Patients With and Without Diabetes Mellitus in the MERLIN-TIMI 36 Randomized Controlled Trial
David A. Morrow, Benjamin M. Scirica, Bernard R. Chaitman, Darren K. McGuire, Sabina A. Murphy, Ewa Karwatowska-Prokopczuk, Carolyn H. McCabe and Eugene Braunwald for the MERLIN-TIMI 36 Investigators

_Circulation_. 2009;119:2032-2039; originally published online April 6, 2009; doi: 10.1161/CIRCULATIONAHA.107.763912
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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