Effects of Ranolazine on Recurrent Cardiovascular Events in Patients With Non–ST-Elevation Acute Coronary Syndromes: The MERLIN-TIMI 36 Randomized Trial

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Context Ranolazine is a novel antianginal agent that reduces ischemia in patients with chronic angina but has not been studied in patients with acute coronary syndromes (ACS).

Objective To determine the efficacy and safety of ranolazine during long-term treatment of patients with non–ST-elevation ACS.

Design, Setting, and Patients A randomized, double-blind, placebo-controlled, multinational clinical trial of 6560 patients within 48 hours of ischemic symptoms who were treated with ranolazine (initiated intravenously and followed by oral ranolazine extended-release 1000 mg twice daily, n = 3279) or matching placebo (n = 3281), and followed up for a median of 348 days in the Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes (MERLIN)-TIMI 36 trial between October 8, 2004, and February 14, 2007.

Main Outcome Measures The primary efficacy end point was a composite of cardiovascular death, myocardial infarction (MI), or recurrent ischemia through the end of study. The major safety end points were death from any cause and symptomatic documented arrhythmia.

Results The primary end point occurred in 696 patients (21.8%) in the ranolazine group and 753 patients (23.5%) in the placebo group (hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.83-1.02; P = .11). The major secondary end point (cardiovascular death, MI, or severe recurrent ischemia) occurred in 602 patients (18.7%) in the ranolazine group and 625 (19.2%) in the placebo group (HR, 0.96; 95% CI, 0.86-1.08; P = .50). Cardiovascular death or MI occurred in 338 patients (10.4%) allocated to ranolazine and 343 patients (10.5%) allocated to placebo (HR, 0.99; 95% CI, 0.85-1.15; P = .87). Recurrent ischemia was reduced in the ranolazine group (430 [13.9%]) compared with the placebo group (494 [16.1%]; HR, 0.87; 95% CI, 0.76-0.99; P = .03). QTc prolongation requiring a reduction in the dose of intravenous drug occurred in 31 patients (0.9%) receiving ranolazine compared with 10 patients (0.3%) receiving placebo. Symptomatic documented arrhythmias did not differ between the ranolazine (99 [3.0%]) and placebo (102 [3.1%]) groups (P = .84). No difference in total mortality was observed with ranolazine compared with placebo (172 vs 175; HR, 0.99; 95% CI, 0.80-1.22; P = .91).

Conclusions The addition of ranolazine to standard treatment for ACS was not effective in reducing major cardiovascular events. Ranolazine did not adversely affect the risk of all-cause death or symptomatic documented arrhythmia. Our findings provide support for the safety and efficacy of ranolazine as antianginal therapy.

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For editorial comment see p 1823.
in this population remains substantial, in particular among those patients with indicators of higher risk, such as diabetes mellitus, ST-segment depression, or a high TIMI risk score.8

Ranolazine is a piperazine derivative that exerts anti-ischemic actions without a clinically significant effect on heart rate or blood pressure.3,9 At clinically relevant concentrations, ranolazine is an inhibitor of the slowly inactivating component of the cardiac sodium current (late INa), which may reduce the deleterious effects associated with the intracellular sodium and calcium overload that accompany and are associated with the intracellular sodium and calcium overload that accompany and may promote myocardial ischemia.7,8 Ranolazine is available as an antiangiogenic agent for patients with chronic angina but has not been studied in patients with ACS or for secondary prevention of major cardiovascular events in patients with established coronary artery disease. Because of an association between ranolazine and prolongation of the QT interval, the safety of the drug has been questioned. Therefore, there is a need for additional safety data to guide its use in patients with coronary artery disease.7 The Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes (MERLIN)-TIMI 36 trial was designed to evaluate the efficacy and safety of ranolazine as a novel intervention to reduce cardiovascular death, myocardial infarction (MI), or recurrent ischemia in the short- and long-term in moderate- to high-risk patients with ACS receiving standard therapy.9

METHODS

Patient Population

Between October 8, 2004, and May 24, 2006, 6560 patients (Figure 1) underwent randomization at 442 sites in 17 countries (list online at http://www.jama.com). The details of the study design have been published previously.9 Eligible patients were aged 18 years or older; had symptoms consistent with myocardial ischemia at rest, lasting for at least 10 minutes and present within the previous 48 hours; and had at least 1 of the following indicators of moderate to high risk of death or recurrent ischemic events: elevated biomarker of necrosis, ST depression of at least 0.1 mV, diabetes mellitus, or an intermediate or high (≥3) TIMI risk score for unstable angina/non–ST-elevation MI.9 Patients were ineligible if they had any of the following major exclusion criteria: cardiogenic shock, persistent ST-segment elevation, successful revascularization of the culprit stenosis before randomization, clinically significant hepatic disease, end-stage renal disease requiring dialysis, treatment with agents known to prolong the QT interval, abnormalities of the electrocardiogram that would interfere with interpretation of Holter monitoring for ischemia, or a life expectancy of less than 12 months.9 Race and ethnicity were self-reported using categories defined by the investigators. The protocol was approved by the relevant institutional review boards at all participating centers. Written informed consent was obtained from all patients.

Study Protocol

The protocol specified that patients were to receive standard treatment for non–ST-elevation ACS and secondary prevention. Eligible patients were randomly assigned in a 1:1 ratio to receive either ranolazine or placebo by a central computerized system using a permuted-block randomization, with stratification according to the responsible physician’s intended initial management strategy (early invasive vs conservative), declared at the time of randomization.

Study medication was to be administered as 200 mg of ranolazine (or matching placebo) intravenously over 1 hour, followed with an 80-mg/h intravenous infusion, which was reduced to 40 mg/h for patients with an estimated creatinine clearance of less than 30 mL/min (<0.50 mL/s), and was continued for 12 to 96 hours. On completion of the infusion, study medication (ranolazine extended-release or matching placebo) was to be continued orally at a dose of 1000 mg twice daily until the end of the study. The protocol specified a reduction in the dose for patients with new renal insufficiency, and for those patients experiencing specific adverse events that may
be treatment related, including persistent prolongation of the QT interval.9 For patients with dose adjustments made during the intravenous infusion, oral study drug was continued at a dose of 750 mg twice daily, 500 mg twice daily, or 375 mg twice daily, based on the final infusion rate.9 The dose could undergo an additional adjustment based on persistence or resolution of the reason for a change.

Patients returned for study visits at 14 days, 4 months, and every 4 months thereafter, until the end of the study. The final day of follow-up was February 14, 2007. During follow-up visits, patients were examined, assessed for adverse events and quality of life, and blood was sampled for local, central laboratory testing, or both. Patients who permanently discontinued the study drug prematurely during the trial were followed up by telephone contact. A digital continuous electrocardiographic Holter monitor for ischemia (Lifecard CF, Delmar Reynolds, Irvine, Calif) was applied to the patient (Lifecard CF, Delmar Reynolds, Irvine, Calif) at the time of randomization and remained in place for 7 days, including after hospital discharge. Exercise tolerance testing was performed at 8 months, or the final visit if it occurred first, in patients able to exercise. The trial was to be continued until at least 310 deaths and 730 major cardiovascular events had been reported to the coordinating center, after which time all patients were requested to return for a final study visit.

End Points
The primary efficacy end point of the trial was the first occurrence of any element of the composite of cardiovascular death, MI, or recurrent ischemia. The major secondary end point was the first occurrence of a major cardiovascular event defined by the composite of cardiovascular death, MI, or severe recurrent ischemia.

Myocardial infarction had to be distinct from the index event and was defined by symptoms suggestive of ischemia/infarction in association with either electrocardiographic, cardiac biomarker, or pathological evidence of infarction using criteria adapted from the definition developed by the American College of Cardiology.9,10 Recurrent ischemia included any of the following: (1) recurrent ischemia with electrocardiographic changes, (2) recurrent ischemia leading to hospitalization, (3) recurrent ischemia prompting revascularization, and (4) worsening of angina/ischemia by at least 1 Canadian Cardiovascular Society class of angina that prompted intensification of antianginal therapy.9 Recurrent ischemia was considered to be severe if any of the first 3 criteria were satisfied.

Other secondary end points included failure of therapy, defined as the composite of cardiovascular death, MI, recurrent ischemia, a positive Holter for ischemia, hospitalization for new or worsening heart failure, or an early positive exercise tolerance test (evidence for ischemia before completing 12 minutes of a modified Bruce protocol or equivalent). Quality of life was assessed as a secondary end point using the anginal frequency and physical limitation scales of the Seattle Angina Questionnaire11 at 4 months of follow-up. The prespecified efficacy end point for assessment of the acute phase through 30 days was the composite of cardiovascular death, MI, severe recurrent ischemia, or a positive Holter for ischemia.

Safety end points included death from any cause, the composite of death from any cause or any cardiovascular hospitalization, the incidence of symptomatic documented arrhythmia, and clinically significant arrhythmias detected during protocol-related Holter monitoring. Symptomatic documented arrhythmias included any symptomatic arrhythmia that led to or prolonged hospitalization or was deemed medically important by the investigator and was documented by any form of electrocardiographic monitoring.

All elements of the primary composite and major secondary efficacy end points, as well as hospitalization for new or worsening heart failure, and symptomatic documented arrhythmia were adjudicated by a blinded clinical events committee.9

Statistical Analyses
The efficacy analysis was a hierarchical testing of the primary followed by the secondary hypotheses in a prespecified order using a closed testing procedure. Once a test result was nonsignificant, analyses of the remaining secondary end points were considered exploratory. This process was designed to ensure preservation of the intended overall type I error for the entire closed test. The trial was designed to have a statistical power of at least 90% to detect a 20% relative risk reduction with ranolazine with respect to the major secondary end point, assuming an incidence of 18% at 1 year in the placebo group.

All efficacy analyses were conducted according to the intention-to-treat principle. The analysis of the primary end point included all primary efficacy events known to have occurred after randomization through the patient’s final study visit. The primary and major secondary efficacy analyses were performed by using the log-rank test stratifying by the intention to use an early invasive strategy. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by using a Cox proportional hazards regression model with effects for treatment and intention for early invasive strategy. Event rates are presented as Kaplan-Meier failure rates at 12 months.

All safety analyses were performed according to the actual treatment received (a single dose or more) by the patient. Periodic assessments of safety were performed by an independent data and safety monitoring board. One planned interim analysis of efficacy based on cardiovascular death was performed by using a Fleming-Harrington-O’Brien12 stopping boundary. The critical 2-sided P value for the primary efficacy analysis, after correction for interim analysis, was .0497.

Our study was an investigator-initiated clinical trial by the TIMI Study Group, designed in conjunction with
the steering committee with review by the trial sponsor. The investigators had free and complete access to the data. Data coordination was performed by the Nottingham Clinical Research Group (list online at http://www.jama.com). The raw database was provided to the TIMI Study Group and all analyses reported in this article were performed independently by the TIMI Study Group (S.A.M.), whose members wrote this article and take responsibility for the data. Validation of the major efficacy and safety analyses was also performed by Nottingham Clinical Research Group (the data coordinating center), as well as by the sponsor. Analyses were conducted by the TIMI Study Group using Stata SE version 9.0 (StataCorp LP, College Station, Tex).

### Results

The 2 groups of patients were well-matched with respect to their baseline characteristics (Table 1). A total of 6303 patients (96.1%) were treated with aspirin, 5926 patients (90.3%) with either unfractionated heparin or a low-molecular-weight heparin, and 955 patients (14.6%) with a glycoprotein IIb/IIIa receptor antagonist. The median time from symptom onset to randomization was 24 hours (interquartile range, 13-34). Study drug was administered intravenously to 6541 patients (99.7%) for a median of 23 hours (interquartile range, 19-29) and followed up with oral administration in 6399 patients (97.5%). The qualifying ACS was managed with medical therapy alone in 3966 patients (60.5%), a percutaneous coronary intervention in 2074 patients (31.6%), and coronary artery bypass graft surgery in 520 patients (7.9%). Concomitant medications were administered to patients during the treatment period as follows: clopidogrel or ticlopidine to 4215 patients (64.3%); β-blockers to 5852 patients (89.2%); calcium channel blockers to 1977 patients (30.1%), including diltiazem to 312 patients (4.8%) and verapamil to 190 patients (2.9%); angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers to 5130 patients (78.2%); and statins to 5404 patients (82.4%). Patients were followed up for up to 24 months, with a median follow-up of 348 days (interquartile range, 236-460). Nine patients (0.1%) were lost to follow-up.

### Efficacy End Points

The primary end point (cardiovascular death, MI, or recurrent ischemia) occurred in 696 patients (21.8%) in the ranolazine group compared with 753 patients (23.5%) in the placebo group (HR, 0.99; 95% CI, 0.83-1.16; P = .50). The major secondary end point (cardiovascular death, MI, or severe recurrent ischemia) occurred in 625 patients (18.7%) in the ranolazine group compared with 753 patients (23.5%) in the placebo group (HR, 0.96; 95% CI, 0.86-1.08; P = .50). Failure of therapy (cardiovascular death, MI, recurrent ischemia, positive Holter for ischemia, hospitalization for new or worsening heart failure, or an early positive exercise...
tolerance test) occurred in 1173 patients (36.8%) in the ranolazine group compared with 1233 patients (38.3%) in the placebo group (HR, 0.94; 95% CI, 0.87-1.02; \(P = .16\)).

Individual elements of the primary end point and failure of therapy end point at 30 days and end of study are shown in Table 2. Ranolazine had no effect on the rate of cardiovascular death or MI, individually or as a composite (Figure 3). However, the cumulative incidence of recurrent ischemia was significantly lower in patients allocated to ranolazine compared with those allocated to placebo (Figure 3). A trend toward an early reduction in recurrent ischemic complications with ranolazine was evident with respect to the 30-day end point of cardiovascular death, MI, severe recurrent ischemia, or positive Holter for ischemia (\(P = .055\)) (Table 2).

An effect of long-term treatment with ranolazine on angina was evident with respect to several prespecified exploratory end points. Worsening angina by at least 1 Canadian Cardiovascular Society Class requiring intensification of medical therapy was less frequent in the ranolazine group (316 [10.6%]) compared with the placebo group (391 [13.0%]; HR, 0.80; 95% CI, 0.69-0.93; \(P = .003\)). A small improvement in anginal frequency with ranolazine was recorded using the Seattle Angina Questionnaire.

**Table 2. Efficacy Outcomes**

<table>
<thead>
<tr>
<th>Event</th>
<th>Ranolazine (n = 3279)</th>
<th>Placebo (n = 3281)</th>
<th>Risk (95% CI)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization to end of study</td>
<td></td>
<td></td>
<td>Hazard Ratio</td>
<td></td>
</tr>
<tr>
<td>Primary end point†</td>
<td>696 (21.8)</td>
<td>753 (23.5)</td>
<td>0.92 (0.83-1.02)</td>
<td>.11</td>
</tr>
<tr>
<td>Major secondary end point‡</td>
<td>602 (18.7)</td>
<td>625 (19.2)</td>
<td>0.96 (0.86-1.08)</td>
<td>.50</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>147 (4.4)</td>
<td>148 (4.5)</td>
<td>1.00 (0.79-1.25)</td>
<td>.98</td>
</tr>
<tr>
<td>MI</td>
<td>235 (7.4)</td>
<td>242 (7.6)</td>
<td>0.97 (0.81-1.16)</td>
<td>.76</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>430 (13.9)</td>
<td>494 (16.1)</td>
<td>0.87 (0.76-0.99)</td>
<td>.03</td>
</tr>
<tr>
<td>With electrocardiographic changes</td>
<td>126 (4.1)</td>
<td>143 (4.7)</td>
<td>0.88 (0.69-1.12)</td>
<td>.31</td>
</tr>
<tr>
<td>Leading to hospitalization</td>
<td>247 (8.0)</td>
<td>279 (8.8)</td>
<td>0.88 (0.75-1.05)</td>
<td>.16</td>
</tr>
<tr>
<td>Leading to revascularization</td>
<td>142 (4.6)</td>
<td>168 (5.3)</td>
<td>0.84 (0.67-1.05)</td>
<td>.13</td>
</tr>
<tr>
<td>Worsening angina</td>
<td>135 (4.2)</td>
<td>175 (5.9)</td>
<td>0.77 (0.62-0.97)</td>
<td>.02</td>
</tr>
<tr>
<td>Failure of therapy§</td>
<td>1173 (36.8)</td>
<td>1233 (38.3)</td>
<td>0.94 (0.87-1.02)</td>
<td>.16</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>141 (4.5)</td>
<td>135 (4.2)</td>
<td>1.05 (0.83-1.33)</td>
<td>.68</td>
</tr>
<tr>
<td>Randomization to 30 d</td>
<td></td>
<td></td>
<td>Relative Risk</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death, MI, severe recurrent ischemia, positive Holter for ischemia</td>
<td>757 (23.1)</td>
<td>824 (25.1)</td>
<td>0.92 (0.84-1.00)</td>
<td>.055</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>57 (1.7)</td>
<td>50 (1.5)</td>
<td>1.14 (0.78-1.66)</td>
<td>.49</td>
</tr>
<tr>
<td>MI</td>
<td>90 (2.7)</td>
<td>114 (3.5)</td>
<td>0.79 (0.60-1.04)</td>
<td>.09</td>
</tr>
<tr>
<td>Severe recurrent ischemia</td>
<td>121 (3.7)</td>
<td>131 (4.0)</td>
<td>0.92 (0.73-1.18)</td>
<td>.52</td>
</tr>
<tr>
<td>Positive Holter for ischemia</td>
<td>613 (19.9)</td>
<td>658 (21.0)</td>
<td>0.93 (0.84-1.04)</td>
<td>.21</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; MI, myocardial infarction.

*Reported values are hazard ratios for randomization to end of study and relative risks for randomization to 30 days. Event rates are Kaplan-Meier failure rates at 12 months. Individuals may have experienced more than 1 event.

†Cardiovascular death, MI, or recurrent ischemia.

‡Cardiovascular death, MI, severe recurrent ischemia.

§Cardiovascular death, MI, severe recurrent ischemia, hospitalization for new or worsening heart failure, positive Holter for ischemia, or an early positive exercise tolerance test.

| Prespecified 30-day end point            |
naire (mean [SD], 84.3 [22.2] in the ranolazine group vs 82.2 [23.2] in the placebo group; P < .001). This difference was greater among those patients who entered the trial with a history of angina (n = 2898) with Seattle Angina Questionnaire data; mean [SD], 79.5 [24.1] in the ranolazine group vs 75.5 [25.3] in the placebo group; P < .001. There was no difference in the physical limitation scale between treatment groups in the overall population (P = .30) or for those patients with prior angina (P = .30).

There was no significant heterogeneity of the effect of ranolazine on the primary end point across the major subgroups examined, including those patients treated with intent for a noninvasive strategy (FIGURE 4). In contrast with previous studies suggesting diminished efficacy on exercise performance in women with stable angina, the effect of ranolazine on the primary end point was significant among women (n = 2291; HR, 0.83; 95% CI, 0.70-0.99), driven by a 29% relative reduction in recurrent ischemia with ranolazine (P = .002), but without definitive statistical evidence of an interaction based on sex (P for interaction = .12). There was no heterogeneity in the effect of ranolazine on recurrent ischemia in those patients treated with an early invasive strategy compared with an early conservative strategy (P for interaction = .52).

### Safety and Tolerability

Death from any cause in the safety analysis population did not differ among patients treated with ranolazine compared with patients treated with placebo (HR, 0.99; 95% CI, 0.80-1.22; P = .91) (TABLE 3). Sudden cardiac death and the composite of death due to any cause or any cardiovascular hospitalization also did not differ in patients treated with ranolazine (56 [1.7%] and 1046 [33.2%], respectively) compared with those patients treated with placebo (65 [1.8%] and 1082 [33.4%], respectively). The incidence of symptomatic documented arrhythmias throughout the duration of the study was similar in patients treated with ranolazine compared with placebo (P = .84). Furthermore, the frequency of clinically significant arrhythmias observed during Holter monitoring (n = 6351) during the first 7 days was lower in the ranolazine group (2330 patients [73.7%]) vs in the placebo group (2650 patients [83.1%]; P < .001). This reduction included a lower incidence of ventricular tachycardia (948 [30%] of 3158 patients vs 1211 [38%] of 3184 patients, respectively; P < .001).

Discontinuation of treatment because of an adverse event, the patient's preference, or for other reasons occurred in 915 patients (28%) in the ranolazine group and 736 patients (22%) in the placebo group (P < .001). Discontinuation due to an adverse event was reported significantly more frequently in patients receiving ranolazine (286 [8.8%]) compared with patients receiving placebo (154 [4.7%], P < .001). During treatment, the dose of study drug was permanently decreased during the intravenous phase due to an adverse event in 63 patients (1.9%) who were treated with ranolazine and 37 patients (1.1%) who were treated with placebo. In addition, in 13 patients (0.4%) in the ranolazine group, the dose was reduced for renal dysfunction; in 31 patients (0.9%), the dose was reduced for persistent prolongation of the QTc; and in 11 patients (0.3%), the dose was reduced for other reasons. In the placebo group, each of these proportions was 9 (0.3%), 10 (0.3%), and 11 (0.3%), respectively.

During chronic treatment with oral study medication, the dose was reduced in 334 patients (10%) receiving ranolazine and in 177 patients (5%) receiving placebo (P < .001). In the ranolazine group, the last dose taken was 1000 mg twice daily in 2715 patients (83%), 750 mg twice daily in 180 patients (6%), 500 mg twice daily in 235 patients (7%), and 375 mg twice daily in 64 patients (2%); 74 patients (2%) never took an oral dose.

The most frequent adverse events, which were not end points, occurred in more than 4% of patients, and were more frequent with ranolazine vs placebo, were dizziness (13% vs 7%), nausea (9% vs 6%), and constipation (9% vs 3%, respectively). There were 109 cases of syncope in the ranolazine group.
(3.3%) and 75 cases in the placebo group (2.3%, P=.01). These cases included events reported as syncpe, vasovagal syncope, and loss of consciousness. The greater number of cases of syncpe in the ranolazine group (n = 34) were largely categorized by the investigators as vasovagal syncope (38 cases vs 18 cases, respectively). Two cases of torsades de pointes were identified by the investigators: 1 in the placebo group and 1 in the ranolazine group.

**COMMENT**

In this trial of patients with non–ST-elevation ACS at moderate to high risk of recurrent cardiovascular events, there was no significant benefit of ranolazine compared with placebo with re-

### Table 3. Major Safety Outcomes*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. (%) of Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>464/2173</td>
<td>21.8</td>
<td>.98 (0.86-1.12)</td>
</tr>
<tr>
<td>Women</td>
<td>232/1106</td>
<td>21.8</td>
<td>.83 (0.70-0.99)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>538/2717</td>
<td>20.3</td>
<td>.93 (0.83-1.05)</td>
</tr>
<tr>
<td>≥75</td>
<td>156/562</td>
<td>29.2</td>
<td>.90 (0.73-1.11)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>431/2175</td>
<td>20.2</td>
<td>.95 (0.84-1.09)</td>
</tr>
<tr>
<td>Yes</td>
<td>265/1104</td>
<td>25.0</td>
<td>.87 (0.74-1.02)</td>
</tr>
<tr>
<td>Prior Angina</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>239/1428</td>
<td>17.4</td>
<td>1.03 (0.86-1.24)</td>
</tr>
<tr>
<td>Yes</td>
<td>443/1789</td>
<td>25.2</td>
<td>.86 (0.75-0.97)</td>
</tr>
<tr>
<td>TIMI Risk Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>300/1820</td>
<td>17.4</td>
<td>1.01 (0.86-1.19)</td>
</tr>
<tr>
<td>4-7</td>
<td>396/1459</td>
<td>27.4</td>
<td>.87 (0.76-0.99)</td>
</tr>
<tr>
<td>Index Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>324/1541</td>
<td>21.4</td>
<td>.94 (0.81-1.09)</td>
</tr>
<tr>
<td>Non–ST-Elevation MI</td>
<td>364/1675</td>
<td>22.4</td>
<td>.92 (0.80-1.06)</td>
</tr>
<tr>
<td>ST-Segment Depression ≥1 mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>416/2137</td>
<td>25.1</td>
<td>.97 (0.85-1.11)</td>
</tr>
<tr>
<td>Yes</td>
<td>280/1142</td>
<td>25.0</td>
<td>.85 (0.73-1.00)</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≥60 mL/min</td>
<td>485/2565</td>
<td>19.2</td>
<td>.90 (0.79-1.01)</td>
</tr>
<tr>
<td>&lt;60 mL/min</td>
<td>208/700</td>
<td>31.5</td>
<td>.98 (0.81-1.19)</td>
</tr>
<tr>
<td>Early Invasive†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>444/1946</td>
<td>23.2</td>
<td>.94 (0.83-1.08)</td>
</tr>
<tr>
<td>Yes</td>
<td>252/1333</td>
<td>19.7</td>
<td>.88 (0.74-1.04)</td>
</tr>
<tr>
<td>Overall</td>
<td>696/3279</td>
<td>21.8</td>
<td>.92 (0.83-1.02)</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; MI, myocardial infarction. To convert creatinine clearance to mL/s, multiply by 0.0167.

*The TIMI risk score was dichotomized at the median, reflecting patients at higher (score 4-7) or lower (score 0-3) risk of death or recurrent ischemic events.

†Intend to manage the patient with an early invasive or conservative management strategy as recorded at the time of randomization.

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spect to the composite end point of cardiovascular death, MI, or recurrent ischemia during a median of 1 year of treatment. Additional analyses revealed a 13% relative reduction in the risk of recurrent ischemia, and fewer increases in other antianginal therapy in patients treated with ranolazine, with no effect on the composite of cardiovascular death or MI. Ranolazine appeared to be safe with no discernable difference from placebo in the prespecified safety end points of symptomatic documented arrhythmias, sudden cardiac death, or death from any cause. Indeed, ranolazine was associated with a significant reduction in the frequency of arrhythmias detected by Holter recording during the first 7 days after randomization. There was more syncope reported with ranolazine, consonant with the prior experience in patients with chronic angina.7

Ranolazine is currently available for the treatment of selected patients with chronic angina who have persistent symptoms despite treatment with B-blockers, calcium channel blockers, or nitrates. Prior studies of ranolazine extended-release have been conducted in patients with confirmed coronary artery disease with ischemic ST-segment depression before completion of 9 minutes on a modified Bruce protocol.5,6 or with at least 3 episodes of angina per week despite treatment with a calcium channel blocker.14 Together these studies demonstrated that ranolazine increases the time to ischemia on treadmill testing, improves exercise duration, and reduces the frequency of angina and use of sublingual nitroglycerin in these highly symptomatic patients.7 Subgroup analyses from these studies (approximately 1500 patients in total) pointed to a possible diminished treatment effect of ranolazine on exercise performance in women.13 Because of a concentration-related increase in the QT interval, the use of ranolazine has been recommended only for patients who have not had an adequate response to other antianginal agents.7 Moreover, the sample size and duration of therapy in these trials were not designed to evaluate the effect of ranolazine for secondary prevention of major cardiovascular events. Experimental data have revealed reductions in the extent of ischemic injury and improved left ventricular performance in animal models with acute MI.13 However, ranolazine had not been studied previously in patients with acute ischemic syndromes.

We enrolled patients during the acute phase of their presentation with ACS and investigated the efficacy of ranolazine for a potential new application in the acute management of ACS as well as for the long-term prevention of major cardiovascular events and recurrent ischemia. The results of this robustly powered, randomized trial do not support the use of ranolazine for acute management of ACS or as disease-modifying therapy for secondary prevention of cardiovascular death or MI. However, our findings suggest a benefit of ranolazine as antianginal therapy in a substantially more broad population of patients with established ischemic heart disease than previously studied. Analyses of subgroups must be interpreted cautiously given the overall nonsignificant primary efficacy result. Nevertheless, in contrast to prior studies based on exercise testing, the reduction in recurrent ischemia with ranolazine was certainly not less in women than in men.

In this large trial that approximately doubles the existing safety experience with ranolazine extended-release, we found that there was no excess of arrhythmias or sudden cardiac death during a median 1-year follow-up in patients treated with ranolazine compared with placebo. There was a higher rate of discontinuation due to adverse events in the ranolazine group, with the most common adverse events being dizziness, nausea, and constipation. This tolerability profile along with the higher proportion of patients with syncope should be considered by the clinician in assessing the potential risks vs benefits of treatment with ranolazine. The etiology of syncope with ranolazine remains unexplained and requires additional study.7 The finding of a significant reduction in arrhythmias detected on Holter monitoring during the first 7 days provides the first clinical evidence for the potential relevance of experimental data showing suppression of markers of proarrhythmia, including early after-depolarizations and transmural dispersion of repolarization with ranolazine,16 and provides some reassurance with respect to arrhythmia as a potential cause for syncope. Nevertheless, awareness with longer term use in the community remains important. The possible anti-arrhythmic effects of ranolazine warrant additional investigation.

The following limitations of our study should be recognized. All of the efficacy analyses reported in this article were prespecified as part of the statistical analysis plan that was finalized before database lock. Given the statistically nonsignificant result for the primary end point, all additional efficacy analyses, although prespecified, should be considered as de facto exploratory. However, particularly when interpreted in the context of prior randomized studies of ranolazine,5,6,14 our observations regarding the efficacy and apparent safety of ranolazine as an antianginal agent contribute to an understanding of its clinical use. The frequency of premature permanent cessation of study drug in our trial is comparable with other contemporary trials of long-term therapy after presentation with ACS.17,18 Premature cessation of study drug would be expected to have biased the intention-to-treat efficacy analysis toward the null result.

CONCLUSIONS

The addition of ranolazine to current standard of care for non–ST-elevation ACS was not effective in reducing the rate of the composite of cardiovascular death, MI, or recurrent ischemia, and is not indicated for the treatment of ACS. The observed reduction in recurrent ischemia in a broad population of patients with established coronary artery disease is consistent with previ-
ous evidence in selected patients with chronic angina. These findings, together with the observed favorable overall profile of safety, provide additional evidence to guide the use of ranolazine as antianginal therapy in patients with chronic angina.

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Independent Statistical Analysis: The investigators had free and complete access to the data. Data coordination was performed by the Nottingham Clinical Research Group (see online appendix). The raw database was provided to the TIMI Study Group and all analyses reported in this manuscript were performed independently by the TIMI Study Group (Ms Murphy), whose members wrote this article and take responsibility for the data. Validation of the major efficacy and safety analyses was also performed by Nottingham Clinical Research (the data coordinating center), as well as by the sponsor. MERLIN-TIMI 36 Study Investigators appear online at http://www.jama.com.

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