Coronary Heart Disease

Clinical Features and Outcomes of Women With Unstable Ischemic Heart Disease

Observations From Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36)

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Background—The pathobiological basis of ischemic heart disease and thus the manifestations and response to therapy can differ between women and men. In prior studies, sex-based treatment differences have been observed with the antiischemic ranolazine, with a possibly diminished effect in women.

Methods and Results—We conducted a prospectively planned analysis of the clinical, biomarker, angiographic, and continuous ECG features and 1-year outcomes of women with unstable ischemic heart disease randomized to ranolazine or placebo in Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36). Compared with men (n=4269), women (n=2291) were older with more risk factors (P<0.001). On presentation, women were less likely than men to have significant epicardial coronary artery disease (no stenosis ≥50% on angiography, 19.4% versus 8.6%; P<0.001) or elevated troponin (57.1% versus 68.9%; P<0.001). Yet, women were more likely to have an elevated B-type natriuretic peptide (47.0% versus 40.2%; P<0.001), worse median angina frequency scores (80 versus 100; P<0.001), and an ischemic episode on continuous ECG administered during the first 7 days (22.5% versus 19.3%; P=0.0025). Women and men were at similar adjusted risk for the primary end point of cardiovascular death, myocardial infarction, or recurrent ischemia (adjusted hazard ratio, 1.11; 95% confidence interval, 0.96 to 1.29; P=0.15). Ranolazine was associated with a significant reduction in recurrent ischemia in women (13.0% versus 18.2%; hazard ratio, 0.71; 95% confidence interval, 0.57 to 0.88; P=0.002).

Conclusions—Women with a clinical syndrome consistent with unstable ischemic heart disease, despite having less obstructive coronary artery disease, were more likely than men to report anginal episodes and had more recorded ischemic periods on continuous ECG. In this setting, ranolazine may be a particularly useful antiischemic agent in women.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00099788.

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Key Words: angina, unstable □ heart disease □ sex □ women

Each year in the United States, more women than men undergo assessment and hospitalization for chest pain.1 Yet when evaluated invasively, in the setting of either stable angina or a presumed non–ST-elevation acute coronary syndrome, women have lower rates of obstructive epicardial coronary disease.2–4 Additionally, experimental and clinical data suggest that women, especially younger women, can present with different structural coronary plaque morphology compared with men.5,6 Despite these anatomical observations, for a given extent of epicardial disease, women have a greater burden of angina than men and experience less relief of symptoms with current therapies.7–8 Whether women have more prominent contributions from microvascular and endothelial dysfunction and exhibit more frequent dysregulation of coronary vasomotor tone continues to be explored.5,5,6,9

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1809
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With this background, we conducted an analysis within the Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial to assess the pathobiologic characteristics and contemporary treatment patterns of 2291 women with ischemic heart disease. In this study, sex-specific clinical, biomarker, and angiographic profiles were evaluated. Additionally, among men and women, we compared the degree of ischemia observed on continuous ECG (cECG) monitoring (using the largest collection of cECG recordings to date) and the degree of angina assessed by the Seattle Angina Questionnaire (SAQ). The relationships between these parameters and cardiovascular outcomes were then evaluated.

Additionally, recognizing the potential for different responses to pharmacological therapy in women and men, we were interested in evaluating the sex-specific antiischemic properties of ranolazine in the MERLIN-TIMI 36 trial. Ranolazine is a novel antianginal that was approved in 2006 in the United States for use in selected patients with chronic angina. The medication improves exercise capacity and reduces angina; however, prior observations suggested that the efficacy of the medication may be smaller in women than men.10–12 This determination was based on 2 studies that in aggregate included 343 women. Therefore, we conducted a prospectively planned analysis within the MERLIN-TIMI 36 trial, which substantially adds to the experience of using ranolazine in women.

Methods

Patient Population and Treatments

MERLIN-TIMI 36 was a multicenter, randomized, double-blind trial that included 6560 subjects from 442 sites in 17 countries.13,14 Eligible patients had at least 10 minutes of ischemic symptoms at rest and presented with one of the following: elevated markers of myonecrosis, ≥0.1-mV ST depression, diabetes mellitus, or an intermediate to high (≥3) TIMI risk score. Exclusion criteria included persistent ST elevation, hepatic disease, dialysis, and ECG features that would limit the interpretation of ischemia on cECG monitoring, including predominantly paced rhythms, left bundle-branch block, left ventricular hypertrophy with strain, and use of digoxin. The protocol was approved by the relevant institutional review boards, and written consent was obtained from all patients.

Patients were randomized in a 1:1 ratio to ranolazine or placebo in addition to standard of care. Ranolazine (or matching placebo) was administered as a 200-mg bolus over 1 hour with an 80-mg/h infusion for 12 to 96 hours. Extended-release 1000 mg oral ranolazine or placebo was to be given twice daily for the remainder of the study. In the case of renal insufficiency, the intravenous and oral dosing of ranolazine was reduced. Participants were evaluated at 14 days, 4 months, and every 4 months until the end of the study. In total, 4 women and 5 men were lost to follow-up by the end of the trial.

Evaluations

At baseline, clinical features were collected, and patients underwent blood testing. Biomarker evaluation was performed for C-reactive protein (Dade-Behring, Deerfield, Ill), cardiac troponin I (Tnl-Ultra, Siemens, Malvern, Pa), and B-type natriuretic peptide (BNP, Siemens). If angiography and/or revascularization was conducted, characteristics of the lesions and interventions were recorded. Quality-of-life assessments were obtained at baseline and 4 months with the SAQ, which has been shown to be a valid and reliable measure in women with coronary disease.15

From the time of randomization to day 7, subjects wore a digital cECG monitor (Delmar and Spacelabs, Issaquah, Wash). The cECG recordings were evaluated by blinded reviewers in the TIMI Core Laboratory, and the results of these recordings were used for research purposes only. The predefined definition of ischemia included ≥0.1-mV ST depression lasting ≥1 minute with a heart rate at onset <100 bpm. Additional arrhythmia end points have been defined previously.13,16

Outcomes

During the course of the study, patients were followed for adverse events and clinical outcomes. For the overall study, the primary clinical end point included a composite of cardiovascular death, myocardial infarction (MI), or recurrent ischemia. MI has been defined in detail.13 Recurrent ischemia included recurrent ischemia with ECG changes, leading to hospitalization, or prompting revascularization or worsening of angina or ischemia by at least 1 Canadian Cardiovascular Society class leading to intensification of antianginal therapy. Components of the primary end point were adjudicated by a blinded clinical events committee.13

Statistical Methods

The characteristics of women and men were compared by use of the Wilcoxon rank-sum test for continuous variables and the χ² test for categorical variables. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with a Cox proportional-hazards regression model. Event rates were determined by Kaplan-Meier failure rates at 12 months. Multivariable models evaluating the association of gender and outcomes were adjusted for baseline variables (age, race, body mass index, creatinine clearance, diabetes mellitus, hypertension, angina, MI, revascularization, heart failure, and smoking status), features on presentation (ST deviation, index event, obstructive epicardial disease, troponin status, and BNP status), and in-hospital treatments (percutaneous coronary intervention, coronary artery bypass grafting, glycoprotein IIb/IIIa receptor inhibitors, thienopyridines, statins, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers). For treatment-specific outcomes, analyses were stratified by the intention to use an early invasive strategy. The interaction between treatment and sex was evaluated within a Cox proportional-hazards model. All analyses reported here were performed independently by the TIMI Study Group using STATA/SE 9.2 (STATA Corp, College Station, Tex). 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

Clinical Features and Biomarker Data

The study included 2291 women (35%) and 4269 men (65%). The baseline TIMI Risk Score was similar between the sexes, with 20.9% of women and 20.1% of men being classified as high risk (score of 5 to 7; Table 1).17 However, the components of risk differed. Specifically, women were more likely to present with a history of cardiovascular risk factors (including hypertension and diabetes mellitus), prior angina episodes, ST depression on their ECGs, and increased age, whereas men were more likely to present with prior coronary artery disease and elevated markers of myonecrosis (P<0.001 for each; Figure 1).

Relative to the biomarker data, the troponin values at baseline were 3.2±12.6 mg/dL for women compared with 6.6±16.9 mg/dL for men (P<0.001). The inverse was true for markers of hemodynamic stress, with women having higher BNP concentrations than men (165.7±297.2 versus...
Table 1. Baseline Characteristics of Women and Men

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Women (n=2291)</th>
<th>Men (n=4269)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67 (59–74)</td>
<td>62 (54–70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age ≥75 y, n/N (%)</td>
<td>539/2291 (23.5)</td>
<td>615/4269 (14.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White, n/N (%)</td>
<td>2154/2291 (94.0)</td>
<td>4087/4269 (95.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75 (65–84)</td>
<td>84 (75–95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29 (25–32)</td>
<td>28 (25–31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>71 (55–91)</td>
<td>89 (69–112)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n/N (%)</td>
<td>920/2291 (40.2)</td>
<td>1300/4269 (30.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n/N (%)</td>
<td>1883/2283 (82.5)</td>
<td>2921/4232 (69.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia, n/N (%)</td>
<td>1405/2057 (68.3)</td>
<td>2645/3941 (67.1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Metabolic syndrome, n/N (%)</td>
<td>658/1371 (48.0)</td>
<td>1136/2969 (38.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker, n/N (%)</td>
<td>325/2289 (14.2)</td>
<td>1351/4267 (31.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior MI, n/N (%)</td>
<td>655/2266 (28.9)</td>
<td>1559/4230 (36.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior revascularization, n/N (%)</td>
<td>471/2288 (20.6)</td>
<td>1273/4267 (29.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior angina, n/N (%)</td>
<td>1333/2244 (59.4)</td>
<td>2232/4199 (53.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior heart failure, n/N (%)</td>
<td>477/2291 (20.8)</td>
<td>618/4269 (14.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI risk score, n/N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>594/2291 (25.9)</td>
<td>1172/4269 (27.5)</td>
<td>0.38</td>
</tr>
<tr>
<td>3–4</td>
<td>1218/2291 (53.2)</td>
<td>2239/4269 (52.4)</td>
<td></td>
</tr>
<tr>
<td>5–7</td>
<td>479/2291 (20.9)</td>
<td>858/4269 (20.1)</td>
<td></td>
</tr>
<tr>
<td>Index event, n/N (%)</td>
<td>1206/2291 (52.6)</td>
<td>1861/4269 (43.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UA</td>
<td>1032/2291 (45.0)</td>
<td>2310/4269 (54.1)</td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>53/2291 (2.3)</td>
<td>98/4269 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from symptoms to randomization, h</td>
<td>24 (13–34)</td>
<td>24 (13–34)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

UA indicates unstable angina; NSTEMI, non–ST-segment elevation MI. Data are presented as median (interquartile range) when appropriate.

*Among those without a history of diabetes mellitus.

116.5±184.9 mg/dL; P<0.001). The relationship between higher BNP values among women persisted after adjustment for hypertension and diabetes mellitus. Likewise, more women than men had elevated BNP values when evaluated as a dichotomous variable (47.0% versus 40.2%; P<0.001). The C-reactive protein concentrations were similar among women (13.1±19.6 mg/L) and men (14.1±21.2 mg/L; P=0.74).

cECG Data

Monitoring with a cECG device was performed in 6355 patients (97%). Of women who underwent testing, 22.5% exhibited evidence of ischemia from 0 to 7 days after enrollment compared with 19.3% of men (P=0.0025). The median duration of ischemia among subjects who had evidence of ischemia on cECG from 0 to 7 days was 146 minutes in women and 106 minutes in men (P=0.004).

In women, in an evaluation of the relationship between the cECG findings and long-term clinical outcomes, higher rates of cardiovascular death and MI over the 1-year follow-up period were seen among women who experienced ≥1 ischemic episodes on cECG monitoring from day 0 to 7 (P<0.001; Figure 2). Women with at least 1 ischemic episode compared with those with no ischemia on cECG were also at increased risk of the primary end point and each of the individual components of the primary end point (primary end point: 32.3% versus 20.9%, P<0.001; cardiovascular death: 9.6% versus 4.1%, P<0.001; MI: 10.0% versus 6.8%, P=0.02; recurrent ischemia: 21.2% versus 13.8%, P<0.001).

The relationship between the detection of ST changes on the cECG and the risk of cardiovascular death, MI, or recurrent ischemia remained significant after adjustment for epicardial coronary artery disease and hypertension, both of which are variables that could influence the assessment of ischemia on cECG (adjusted HR, 1.45; 95% CI, 1.10 to 1.92; P=0.009). Additionally, the risks of cardiovascular death, MI, or recurrent ischemia associated with ST changes on cECG versus no ST changes on cECG were similar among women with and without evidence of obstructive epicardial disease (with coronary artery disease [CAD]: 32.6% versus 24.3%; HR, 1.43; 95% CI, 1.07 to 1.91; and without CAD: 18.6% versus 8.7%; HR, 1.75; 95% CI, 0.65 to 4.73; Pinteraction=0.66). Likewise, there was no statistical difference in the relationship between cardiovascular death, MI, or recurrent ischemia and cECG ischemia among women with and without hypertension (Pinteraction=0.22).

Interventional and Medical Therapies During the Index Hospitalization

Compared with men, women underwent fewer cardiac procedures during their index hospitalization (Table 2). After adjustment for baseline features (including age, weight, creatinine clearance, prior MI, prior revascularization, index event, ST depression, TIMI Risk Score, troponin), women remained less likely to undergo angiography compared with men (adjusted OR, 0.76; 95% CI, 0.65 to 0.87; P<0.001). On angiographic evaluation, 19.4% of women and 8.6% of men had no evidence of obstructive epicardial disease (at least 1 lesion ≥50%). When the population was restricted to those patients with documented evidence of obstructive coronary disease on angiography (n=3459), women and men underwent percutaneous coronary intervention at similar rates (P=0.71). Women with obstructive epicardial disease on angiography had higher rates of cardiovascular death during the course of the study (4.2% versus 1.1%; P=0.02) and more ischemia on cECG (24.3% versus 13.6%; P<0.001) compared with women without this parameter. Yet, the incidence of worsening angina did not differ between women with and without obstructive epicardial disease (P=0.24).
During the treatment phase and at hospital discharge, women were less likely than men to receive treatment with antiplatelet agents, including glycoprotein IIb/IIIa receptor inhibitors and thienopyridines ($P<0.001$ for each; Table 2). However, among patients who underwent percutaneous coronary intervention, the use of antiplatelet agents in women and men was similar (glycoprotein IIb/IIIa receptor inhibitors: $29.8\%$ versus $34.3\%$, $P=0.051$; thienopyridines: $97.4\%$ versus $98.2\%$, $P=0.26$). Fewer women were prescribed statins after their acute ischemic event. Conversely, women were more likely to receive treatment with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker ($80.4\%$ versus $77.0\%$; $P=0.001$).

Seattle Angina Questionnaire
During the course of the study, quality of life was more severely impaired among women. When the SAQ was administered at baseline, women compared with men had worse physical limitation scores (median, $53$ versus $69$; $P<0.001$), where lower scores indicate more limitation. At 4 months, women continued to report more severe physical limitation than men ($67$ versus $81$; $P<0.001$, restricted to the placebo group). This observation was maintained after adjustment for baseline clinical variables, features on presentation, and in-hospital treatments ($P<0.001$). Women were also found to have worse median angina frequency scores ($80$ versus $100$; $P<0.001$, restricted to placebo group) at 4 months and after adjustment ($P<0.001$).

Clinical Outcomes
Women experienced higher absolute rates of cardiovascular death than men ($5.3\%$ versus $4.0\%$ at 1 year; HR, $1.29$; $95\%$ CI, $1.02$ to $1.63$; $P=0.03$). In our study, this higher absolute risk was explained by age, other clinical characteristics, and medical therapies (eg, statins, antiplatelet agents) given that, after adjustment for these features, there was no significant sex-based difference in cardiovascular mortality (adjusted HR, $0.82$; $95\%$ CI, $0.60$ to $1.12$; $P=0.22$). Both the unadjusted and adjusted rates of the primary end point, MI, and recurrent ischemia were also similar among the sexes (Figure 1).

Figure 1. Features of women and men presenting with unstable ischemic heart disease. Moderate to high TRS indicates a TIMI risk score $\geq3$. HTN indicates hypertension; Revasc, revascularization; and troponin positive, troponin I $\geq0.04$ ng/mL.

Figure 2. Cumulative incidence of cardiovascular death or myocardial infarction among women by ischemia detected on cECG monitoring.
with ranolazine was associated with a significant 29% reduction in recurrent ischemia in women (HR, 0.71; 95% CI, 0.57 to 0.88; P = 0.002) with a P_{interaction} of 0.024 pertaining to the relationship between treatment and sex (Figure 4). There was no significant reduction in cardiovascular death or MI associated with treatment with ranolazine versus placebo among women or men (P_{interaction} = 0.80 and 0.41, respectively).

Additionally, we found consistent findings for the effect of ranolazine versus placebo on performance on exercise testing at 8 months in patients with prior angina among women and men: time to angina (6.5% and 7.9% increase; P_{interaction} = 0.32), total exercise duration (3.5% and 8.1% increase; P_{interaction} = 0.36), and time to 1-mm ST depression (6.3% and 8.0% increase; P_{interaction} = 0.29). Likewise, among women, treatment with ranolazine compared with placebo was associated with less angina as evaluated by the SAQ (values at 4 months: median, 90 versus 80; P < 0.001), with lower values indicating worse angina. Fewer women treated with ranolazine needed to undergo intensification of their antianginal medical regimen (10.4% versus 14.4%; P = 0.003). Relative to safety, there was no difference in symptomatic documented arrhythmias in women treated with ranolazine versus placebo (2.6% versus 2.6%; P = 0.95), and treatment with ranolazine was associated with fewer episodes of ventricular arrhythmias (≥8 beats: 3.6% versus 6.0%; P = 0.008).

### Discussion

Using multiple modalities, including clinical, biomarker, angiographic, SAQ, and cECG monitoring data, this study evaluated the pathobiological characteristics and contemporary treatment strategies in >2000 women with unstable ischemic heart disease. Consistent with prior observations, we found that women with a clinical syndrome consistent with ischemia, despite having less obstructive epicardial CAD than men, were more likely to report a history of angina and equally likely to suffer major adverse outcomes such as cardiovascular death. Extending these findings, we were able to further demonstrate that women also had more documented ischemic episodes than men on cECG monitoring. Furthermore, in the MERLIN-TIMI 36 trial, which serves as the largest assessment of ranolazine in women to date, women experienced at least as much antiischemic efficacy from ranolazine as men. Thus, our findings have potential implications for understanding and caring for the approximately 5.5 million women in the United States with angina.18

### Presentation of Women With Unstable Ischemic Heart Disease

Whereas baseline risk, as assessed by the TIMI Risk Score, was similar among women and men, the components of risk differed. In accordance with prior observations, women were significantly older than the men in this study with more traditional cardiovascular risk factors.19,20 Specifically, women exhibited higher rates of diabetes mellitus and hypertension. Additionally, women were more likely to have evidence of ST depression on their presenting ECG and elevated concentrations of BNP, a marker of hemodynamic stress. Yet, women were less likely to have elevated markers

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### Table 2. Interventional and Medical Treatments

<table>
<thead>
<tr>
<th>Medications*</th>
<th>Women (n=2291), n/N (%)</th>
<th>Men (n=4269), n/N (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2195/2291 (95.8)</td>
<td>4108/4269 (96.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Heparin</td>
<td>2060/2291 (89.9)</td>
<td>3866/4269 (90.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>GPIIb/IIIa receptor inhibitor</td>
<td>255/2291 (11.1)</td>
<td>700/4269 (16.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>1298/2291 (56.7)</td>
<td>2917/4269 (68.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-blocker</td>
<td>2041/2291 (89.1)</td>
<td>3811/4269 (89.3)</td>
<td>0.82</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>1843/2291 (80.4)</td>
<td>3287/4269 (77.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>1786/2291 (78.0)</td>
<td>3618/4269 (84.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic treatments†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>276/846 (32.6)</td>
<td>302/1182 (25.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral agents</td>
<td>451/846 (53.3)</td>
<td>676/1182 (57.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diet alone</td>
<td>104/846 (12.3)</td>
<td>149/1182 (12.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>None</td>
<td>15/846 (1.8)</td>
<td>55/1182 (4.7)</td>
<td></td>
</tr>
</tbody>
</table>
of myonecrosis. Furthermore, we found that nearly 1 in 5 women presenting with unstable ischemic symptoms did not have significant angiographic disease at presentation. These observations, in conjunction with prior work, underscore the possibility of gender-related pathophysiological differences among women and men who present with symptoms consistent with unstable coronary syndromes. Further investigations will be helpful to assess whether these different presentations represent distinct syndromes along a spectrum of CADs.

Ischemia and Angina
To the best of our knowledge, this study includes the largest reported collection of cECG assessments for ischemia in women after unstable ischemic heart disease. During the 7 days of monitoring, more women than men had ischemia on their cECG despite less epicardial disease on angiography. Moreover, when women did have ischemic episodes, they were longer in duration. These differences were not explained by any disparity in the use of revascularization because no sex-based differences in the rates of percutaneous coronary intervention were detected when the population was restricted to those patients with obstructive epicardial disease.

It has been suggested that the detection of ischemia may be complicated in women because of a digoxin-like effect of estrogen, leading to an increased false-positive assessment. Although the median age of women in this study was 67 years and only 1% of the women were on hormone replacement...
therapy, these women would still have more circulating estrogen than men.23 Women also exhibit more vasomotor dysregulation, which could affect the eCG findings. Nevertheless, the increased frequency and duration of ischemia noted in women in MERLIN-TIMI 36 were determined to be associated with worse long-term outcomes, and women with ≥1 episodes of ischemia experienced a 2-fold increase in long-term cardiovascular mortality. These findings indicate that the detection of ischemia in women was not simply an ECG artifact but instead suggestive of a manifestation of myocardial ischemia.

Additionally, during the course of the trial, women were found to have a higher burden of symptomatic angina. On entering the study, more women than men had a history of anginal symptoms and women’s quality of life was more severely impaired as assessed by the SAQ. The excess of angina experienced by women was highlighted in a meta-analysis, which reported a pooled sex ratio of 1.20.24 The study, which included cases from 31 countries and 74 populations, demonstrated that the higher prevalence of angina in women was consistent across region and time. Notably, both premenopausal and postmenopausal women had more chest pain symptoms than men, suggesting that factors beyond hormonal status are relevant to angina burden.25

The higher rates of ischemia and angina among women in our study despite less epicardial CAD have potentially important clinical and pathobiological implications. In our analysis and others, women with chest pain and presentations consistent with unstable ischemic heart disease were found to have less epicardial coronary disease on angiography than men. In the Global Unstable Angina Registry and Treatment Evaluation (GUARANTEE) Registry, for example, 25% of women had no significant coronary disease on catheterization after unstable angina or non–ST-elevation MI compared to 14% of men (P = 0.001).26 Yet, 20% of women with chest pain and no significant epicardial disease have evidence of stress-induced myocardial ischemia,27 which has been associated with worse cardiovascular outcomes.28 Likewise, in our study, we found that >10% of women with no significant obstructive coronary disease had ischemic episodes on follow-up eCG monitoring.

Thus, women’s degree of ischemia observed on eCG monitoring and anginal symptoms recorded on the SAQ may be related to microvascular disease.29 Endothelial dysfunction may also be contributing to the ischemic symptoms experienced by women, especially considering the higher prevalence of hypertension.29 The optimal triage and treatment of these women with microvascular and endothelial dysfunction is still being explored. However, our findings reinforce the need for careful consideration of women with ischemic symptoms even in the absence of significant epicardial disease.

Outcomes of Women With Unstable Ischemic Heart Disease
Although women experienced higher absolute rates of cardiovascular death than men, this risk appears to be related to other confounding factors. Indeed, despite the clinical, bi-

omarker, medication, and eCG differences, as well as the lower prevalence of obstructive epicardial CAD, observed among women and men, after adjustment for baseline clinical features, women had rates of cardiovascular mortality similar to those of men. The same held true for the adjusted rates of the primary end point, MI, and recurrent ischemia.

Several prior analyses have also found that after acute ischemic syndromes women and men have similar rates of death and cardiovascular outcomes after baseline clinical differences are taken into account. In TIMI IIIb, sex was not an independent predictor of death or recurrent MI after non–ST-elevation acute coronary syndrome in a multivariable model that included baseline variables.19 Likewise, in the development of the Global Registry of Acute Coronary Events (GRACE) risk score (used to evaluate the mortality risk after acute coronary syndrome) and the TIMI risk score (used to evaluate the mortality, MI, or severe recurrent ischemia requiring urgent revascularization risk after unstable angina and non–ST-elevation MI), sex was not an independent predictor of poor outcomes.17,30 Thus, whereas some studies have found female sex to be protective after an acute presentation for ischemic coronary disease,20,31 our analysis and other studies suggest that the risk of adverse cardiovascular outcomes after unstable coronary disease are similar among women and men.

Treatment With Ranolazine
Comments from the Food and Drug Administration have suggested that the efficacy of ranolazine may be smaller in women than men on the basis of the Efficacy of Ranolazine in Chronic Angina (ERICA; n = 158 women) and Combination Assessment of Ranolazine in Stable Angina (CARISA; n = 185 women) trials.10–12 In the present analysis, we were able to incorporate the evaluation of >2000 women. Additionally, MERLIN-TIMI 36, in contrast to ERICA and CARISA, was designed to assess hard clinical outcomes over 1 year, including death and ischemic complications. We observed that, consistent with the overall trial, there was a significant reduction in recurrent ischemia associated with treatment with ranolazine versus placebo in conjunction with standard of care in women, with no significant reduction in cardiovascular death or MI. Of note, the P value testing for the interaction of treatment and sex on recurrent ischemia was 0.024, suggesting a greater effect of ranolazine in women; however, considering the multiple tests being performed, the most prudent interpretation would suggest that the antiischemic effects of ranolazine are at least as beneficial in women as in men. Furthermore, we found that women treated with ranolazine compared with placebo reported less angina and required less intensification of their antianginal medical regimen. Thus, the totality of the data, now including MERLIN-TIMI 36, suggests that ranolazine is an efficacious antianginal in women with ischemic heart disease.

Study Limitations
First, in the context of a trial that was neutral in terms of the primary end point, all additional efficacy analyses, including this one, must be regarded as exploratory. However, sex was a prespecified subgroup based on prior data and possible
sex-based differences raised by the Food and Drug Administration. Second, the angiographic evaluations were performed by the investigators, and in this study, the films were not reviewed by an angiographic core laboratory. Third, although this study provides new information on sex and the use of ranolazine in the setting of ischemic heart disease, it does not provide direct experimental observations relative to the underlying mechanisms of this treatment in women.

Conclusions

Women with a clinical syndrome consistent with unstable ischemic heart disease were less likely than men to have obstructive epicardial CAD, yet they were more likely to report angina and to have ischemia on eCEG. Additionally, this study substantially increases the experience of ranolazine in women and indicates that women experience at least as much anti ischemic efficacy from this novel antianginal as men. Considering these findings together, ranolazine may be a particularly useful medication in women with ischemic heart disease.

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Disclosures

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References


CLINICAL PERSPECTIVE

Sex differences in some of the mechanisms of ischemic heart disease exist, and as a result, the presentations and responses to therapy can differ between women and men. Thus, we first conducted a prospectively planned analysis of the clinical, biomarker, angiographic, Seattle Angina Questionnaire, and continuous ECG monitoring data in the Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes—Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial to evaluate the characteristics and contemporary treatment strategies in >2000 women with unstable ischemic heart disease. The findings suggested that despite having less obstructive epicardial coronary disease detected during angiography, women were more likely than men to report anginal episodes and had more recorded ischemic periods on continuous ECG. Second, recognizing the potential for different responses to pharmacological therapy in women and men, we were interested in evaluating the sex-specific antischemic properties of ranolazine in the MERLIN-TIMI 36 trial. In prior, smaller studies, sex-based treatment differences have been observed with ranolazine, with a possibly diminished effect in women. However, in MERLIN-TIMI 36, which serves as the largest assessment of ranolazine in women to date, we found that ranolazine may be a particularly efficacious antischemic agent in women.
Clinical Features and Outcomes of Women With Unstable Ischemic Heart Disease: Observations From Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36)

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