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## Serum potassium levels, cardiac arrhythmias, and mortality following non-ST-elevation myocardial infarction or unstable angina: insights from MERLIN-TIMI 36

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### Abstract

**Background**—In acute coronary syndrome (ACS), potassium levels  $<3.5$  mEq/L are associated with ventricular arrhythmias. Current guidelines therefore recommend a potassium target  $>4.0$  mEq/L in ACS. Our study evaluated the association between potassium levels, cardiac arrhythmias, and cardiovascular death in patients with non-ST-segment elevation myocardial infarction or unstable angina.

**Methods**—Potassium levels were measured in 6515 patients prior to randomization to receive either ranolazine or a placebo in the MERLIN-TIMI 36 trial. A seven-day continuous electrocardiographic assessment was obtained to determine the incidence of non-sustained ventricular tachycardia (NSVT) and ventricular pauses. The association between potassium levels and cardiovascular death was evaluated using a Cox proportional hazards regression model with multivariable adjustment.

**Results**—NSVT lasting for at least eight consecutive beats occurred more frequently at potassium levels  $<3.5$  mEq/L than at potassium levels  $\geq 5$  mEq/L (10.1 vs. 4.5%,  $p=0.03$  for trend), whereas the inverse pattern was observed for ventricular pauses  $>3$  s, which occurred more frequently at potassium levels  $\geq 5$  mEq/L than at potassium levels  $<3.5$  mEq/L (5.9 vs. 2.0%,  $p=0.03$  for trend). There was a U-shaped relationship between the potassium level at admission and both early and late risk of cardiovascular death. Compared with patients with potassium levels

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### Conflict of interest

Ravi B Patel, Sara Tannenbaum, Ana Viana-Tejedor, Jianping Guo, and KyungAh Im have nothing to disclose.

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of 3.5 to <4 mEq/L, a potassium level <3.5 mEq/L was associated with an increased risk of cardiovascular death at day 14 (2.4 vs. 0.8%, HR<sub>adj</sub> 3.1,  $p=0.02$ ) and at one year (6.4 vs. 3.0%, HR<sub>adj</sub> 2.2,  $p=0.01$ ). The risk of cardiovascular death at one year was also significantly increased at potassium levels  $\geq 4.5$  mEq/L and a similar trend was noted at potassium levels  $\geq 5$  mEq/L.

**Conclusions**—The lowest risk of cardiovascular death was observed in patients with admission potassium levels between 3.5 and 4.5 mEq/L. Both lower and higher levels of potassium were associated with tachyarrhythmias and bradyarrhythmias, suggesting a potential mechanistic explanation for the increased risk of cardiovascular death at the extremes of potassium homeostasis.

## Keywords

Arrhythmias; acute coronary syndrome; potassium levels; myocardial infarction; cardiovascular death; ventricular tachycardia

## Introduction

Potassium has an essential role in maintaining myocardial electrical stability. Hypokalemia was first noted to decrease the fibrillation threshold in rabbit hearts over 60 years ago.<sup>1</sup> In the setting of myocardial ischemia, adrenergic stimulation activates the Na–K ATPase pump, lowering plasma potassium levels.<sup>2</sup> Several small, observational studies have suggested that in the setting of acute coronary syndrome (ACS), hypokalemia, typically defined as potassium levels <3.5 mEq/L, is associated with ventricular arrhythmias.<sup>3–9</sup> As a result, both professional guidelines and experts have recommended a target potassium level of at least 4.0 mEq/L in the setting of ACS.<sup>10–12</sup> However, the body of evidence behind this recommendation predates several advances in the management of ACS that are known to reduce the risk of ventricular arrhythmias, specifically the routine use of  $\beta$  blockers and early reperfusion strategies. Two contemporary retrospective cohort studies of patients post-myocardial infarction (MI) observed the lowest in-hospital and three-year mortality rates in patients whose potassium levels were between 3.5 and 4.5 mEq/L.<sup>13,14</sup> These studies therefore challenge prior recommendations of a potassium target >4.0 mEq/L in the setting of ACS.<sup>15</sup> To further explore the risks of hypokalemia, we evaluated the association between potassium levels, mortality, and the incidence of arrhythmias in a well-characterized cohort of patients with non-ST-segment elevation ACS (NSTEMI-ACS), defined as patients with non-ST-segment elevation MI (NSTEMI) or unstable angina (UA).

## Methods

### Patient population

The design and 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 have been reported previously.<sup>16</sup> Patients eligible for enrollment had at least 10 minutes of ischemic symptoms at rest and presented with one of the following additional risk indicators: elevated levels of biomarkers of myonecrosis, ST-segment depression  $\geq 0.1$  mV, a history of diabetes mellitus, or an intermediate to high ( $\geq 3$ ) TIMI risk score. Of the 6560 patients enrolled in MERLIN-TIMI 36, 4252 patients had their

current generation sensitive troponin I (TnI-Ultra, Seimens) levels drawn. NSTEMI was defined as TnI-Ultra levels above the 99th percentile,  $\geq 0.04$   $\mu\text{g/L}$ . Patients with troponin I levels  $< 0.04$   $\mu\text{g/L}$  were categorized as UA. Patients were excluded if they had end-stage renal disease requiring dialysis, cardiogenic shock, or a life expectancy of less than one year. Patients were randomized in a 1:1 ratio to receive either ranolazine or placebo. The protocol was approved by the institutional review boards of our institution and written consent was obtained from all patients.

### Serum potassium measurements and endpoints

Potassium levels obtained prior to randomization were used for the analysis. Patients were categorized into five different potassium groups:  $< 3.5$ ; 3.5 to  $< 4$ , 4 to  $< 4.5$ ; 4.5 to  $< 5$ ; and  $\geq 5$  mEq/L. As described previously, continuous electrocardiographic (cECG) Holter monitors (Lifecard CF, Delmar Reynolds, Irvine, CA, USA) were applied to patients on randomization and remained in place for seven days.<sup>16,17</sup> All cECG recordings were analyzed at the TIMI Electrocardiographic Core Laboratory (Boston, MA, USA). Arrhythmias were identified using a commercially available arrhythmia software program (Pathfinder, Spacelabs Healthcare) that used a combined automated and interactive detection technique. Non-sustained ventricular tachycardia (NSVT) was defined as at least four consecutive ventricular beats with a rate  $> 100$  beats per minute. Episodes were further categorized according to a pre-specified analysis plan as lasting at least eight consecutive beats. Ventricular pauses were defined as any absence of a QRS complex for at least 3 s. An independent committee that was unaware of the treatment assignment adjudicated all deaths as cardiovascular or non-cardiovascular.

### Statistical analysis

Of the 6560 patients enrolled in MERLIN-TIMI 36, 6515 (99%) patients had the requisite Holter and potassium data and were included in this analysis. The baseline characteristics for this patient cohort stratified by potassium level were compared using the Kruskal–Wallis test for continuous variables and the  $\chi^2$  test for categorical variables. The association between the incidence of arrhythmias (NSVT or pauses) and potassium levels was analyzed in the total population by the Cochran–Armitage test. In addition, the following subgroups were analyzed for the incidence of arrhythmias and potassium levels: (1) patients with NSTEMI and UA; (2) patients with a prolonged QTc interval defined as  $\geq 450$  ms; and (3) patients with ischemia detected on cECG monitoring. These analyses were also assessed using the Cochran–Armitage test. The comparison of the incidence of arrhythmias (NSVT or pauses) between the ranolazine and placebo groups was assessed using the  $\chi^2$  test. Event rates at 14 days and one year were calculated by the Kaplan–Meier method. The associations between each group of potassium level and 14-day and one-year mortality were evaluated using a Cox proportional hazards regression model presented as hazards ratios and adjusted for the variables in the TIMI risk score<sup>18</sup> (age  $\geq 65$  years of age, documented coronary artery disease, recent severe angina, ST-segment deviation  $> 0.5$  mm, prior treatment with aspirin, positive cardiac biomarkers, at least three cardiac risk factors (diabetes mellitus, current cigarette smoking, hypertension, hypercholesterolemia, and family history of coronary artery disease)) and also for creatinine clearance, history of congestive heart failure, and coronary angiography at the index hospitalization. Analyses were performed using SAS version 9.3

(SAS Institute Inc., Cary, NC, USA).  $p < 0.05$  (two-tailed) was considered to indicate statistical significance. The authors had full access to, and take full responsibility for, the integrity of the data.

## Results

### Patient characteristics and potassium levels

The baseline patient characteristics by potassium category are presented in Table 1. Potassium levels were collected prior to randomization, which occurred on average  $< 24$  h after the onset of ischemic symptoms and thus represent an early assessment of potassium levels. The median and mean potassium levels were 4.2 mEq/L (interquartile range (IQR) 3.9–4.5) and 4.22 mEq/L (SD 0.51), respectively. The distribution of potassium levels was normally distributed (Figure 1). Patients with hyperkalemia ( $\geq 5.0$  mEq/L) were more likely to have diabetes, heart failure, reduced creatinine clearance, and prior MI ( $p < 0.001$  for all comparisons; Table 1). Patients with potassium  $< 3.5$  mEq/L were more likely to have NSTEMI than UA, to have received glycoprotein IIb/IIIa inhibitors, and to have had a coronary angiogram during hospitalization ( $p < 0.001$  for all comparisons).

### Serum potassium levels and arrhythmias

The median number of days between admission potassium level and the detected of arrhythmia on cECG was 2.5 (IQR 1.4–4.4) for NSVT  $\geq 8$  beats and 2.3 days (IQR 1.2–4.3) for pauses  $\geq 3$  s. Among the entire cohort, there was a stepwise increase in the rate of NSVT lasting at least eight beats in patients with lower levels of potassium, ranging from a rate of 4.5% in patients with a potassium level  $\geq 5.0$  mEq/L to 10.1% in patients with a level  $< 3.5$  mEq/L ( $p = 0.03$  for trend) (Figure 2(a)). There was no relationship between shorter episodes of NSVT and levels of potassium (data not shown). The pattern of an inverse relationship between potassium levels and NSVT  $\geq 8$  beats was similar in patients with NSTEMI and in patients with UA, although the relationship did not reach statistical significance in either subgroup due to the smaller sizes (Table S1). In addition, a similar overall pattern between potassium levels and NSVT  $\geq 8$  beats was noted in patients with both normal ( $< 450$  ms) and prolonged ( $\geq 450$  ms) QTc, and in patients with and without ischemia noted on cECG monitoring (Table S1).

The trend for pauses  $\geq 3$  s followed the opposite pattern to that of ventricular arrhythmias. The lowest rate of pauses (2.0%) was in patients with potassium levels  $< 3.5$  mEq/L and the highest (5.9%) was in patients with potassium levels  $\geq 5.0$  mEq/L ( $p = 0.03$  for trend) (Figure 2(b)). The pattern was similar in all subgroup analyses, although several trends did not reach statistical significance based on smaller sample sizes (Table S2).

The relationship between potassium levels and arrhythmias was similar in patients treated with ranolazine or with the placebo. Overall, patients treated with ranolazine tended to have fewer episodes of tachyarrhythmias or bradyarrhythmias than patients treated with placebo, regardless of the baseline levels of potassium (Figure 3(a) and 3(b)). This relationship was true for both patients with NSTEMI and patients with UA (data not shown).

## Serum potassium levels and cardiovascular death

There was an overall U-shaped relationship between potassium levels and cardiovascular death at day 14 (Figure 4(a)). Compared with the reference group (3.5 to <4 mEq/L), the mortality rates were significantly higher for patients with potassium levels <3.5 mEq/L (0.8 vs. 2.4%,  $HR_{adj}$  3.1, 95% confidence interval (CI) 1.2–8.1,  $p=0.02$ ). There was no significant difference in cardiovascular death between the reference group (3.5 to <4 mEq/L) and the remaining groups (Figure 4(a)). The one-year cardiovascular death rates followed a similar U-shaped relationship across potassium levels. Compared with the reference group (3.5 to <4 mEq/L), mortality rates were significantly higher for patients with potassium levels between 4.5 and 5 mEq/L (3.0 vs. 6.2%,  $HR_{adj}$  1.7, 95% CI 1.1–2.4,  $p=0.01$ ), and even higher for those with potassium levels <3.5 mEq/L (Figure 4(b)). Patients with potassium levels  $\geq 5.0$  mEq/L had a trend toward increased risk of one-year cardiovascular death compared with the reference group ( $HR_{adj}$  1.6, 95% CI 0.99–2.5,  $p=0.06$ ).

## Discussion

In this analysis of over 6500 patients with NSTEMI-ACS, we found that, after adjustment for baseline clinical characteristics, there was a U-shaped relationship between levels of potassium and short- and long-term risk of cardiovascular death. The lowest risk of death was observed in patients with potassium levels between 3.5 and 4.5 mEq/L, whereas the highest risk was seen in patients with either hypokalemia (<3.5 mEq/L potassium) or hyperkalemia ( $\geq 4.5$  mEq/L potassium). Interestingly, the risk of ventricular tachycardia and bradycardic events was associated with potassium levels, but were inversely related to each other, suggesting arrhythmogenic instability at either end of the potassium range and thus identifying 3.5–4.5 mEq/L as the most electrically stable range. This bimodal distribution of arrhythmic risk may explain the U-shaped relationship between potassium levels and early cardiovascular death. Treatment with ranolazine, an anti-angina drug with anti-arrhythmic properties, reduced the risk of both tachyarrhythmias and bradyarrhythmias across the range of potassium levels.

Most studies reporting an association between hypokalemia and arrhythmic death in ACS predate the era of reperfusion and widespread use of  $\beta$  blockers and, in general, included relatively small patient populations.<sup>3–9</sup> Nonetheless, these studies, together with animal models, were the basis for the common practice of targeting potassium levels of 4.0–5.0 mEq/L in the setting of ACS.<sup>10,11</sup> Since these recommendations were published, two retrospective cohort studies have challenged the benefit of consistently targeting potassium levels  $>4.0$  mEq/L. Goyal et al.<sup>13</sup> noted a lower in-hospital mortality in a cohort of over 30,000 patients post-MI with potassium levels of 3.5–4.5 mEq/L. Subsequently, Choi et al.<sup>14</sup> noted similar findings in a cohort of over 2000 patients in South Korea. Our present study of over 6000 patients supports the conclusion that potassium levels  $>4.0$  mEq/L are associated with increased cardiovascular risk. In addition to the increased risk of in-hospital mortality noted by Goyal et al.,<sup>13</sup> our study also suggested that potassium levels  $>4.5$  mEq/L are associated with increased long-term cardiovascular mortality at one year, even after adjusting for other risk factors. In theory, the optimum potassium repletion strategy would

be identified via a randomized controlled trial; however, such trials are unlikely to be feasible given the cost and complexity of an adequately powered trial.

This study provides new insights into the different arrhythmic complications associated with hypo- and hyperkalemia. Consistent with prior studies, lower levels of potassium were clearly associated with higher rates of longer episodes of NSVT. Not surprisingly, the presence of a prolonged QTc interval and hypokalemia were associated with the highest incidence of NSVT. Conversely, elevated levels of potassium were associated with an increased risk of significant bradyarrhythmias. Hyperkalemia is known to decrease ventricular excitability and precipitate complete heart block and sinus arrest.<sup>19</sup> Emerging treatments with novel potassium binders may improve the management of hyperkalemia in the acute setting.<sup>20,21</sup> The proximity in timing between potassium levels at admission and arrhythmias further substantiates the arrhythmic potential at either end of the potassium range. It is possible that arrhythmic complications at either end of the potassium range account for the U-shaped curve of cardiovascular mortality.

Management of NSTEMI-ACS has advanced substantially over the past 20 years. With the broad utilization of  $\beta$  blockers in ACS, the rates of ventricular arrhythmias and mortality have decreased significantly, probably through the suppression of hypokalemia-induced ventricular arrhythmias.<sup>2,22–24</sup> In addition to  $\beta$  blockers, reperfusion with percutaneous coronary intervention, robust antiplatelet treatments, and the creation of cardiac care units have substantially decreased the risk of malignant ventricular arrhythmias and death. In some studies, the risk of ventricular fibrillation in the setting of ACS has decreased by at least one-third over this time period.<sup>25,26</sup> As a result, the magnitude of potassium repletion required to prevent adverse events may not be as substantial. Although it is not possible to determine a causal relationship from our study, our findings raise the possibility that aggressive potassium repletion may even be associated with increased risk.

There are several limitations to our study. As a selected population enrolled in a clinical trial, these results may not be generalizable to all patients with NSTEMI-ACS. Potassium repletion and serial potassium levels during hospitalization were not captured and thus we cannot evaluate the relationships between supplemental potassium or serial potassium levels and outcomes. Determining whether a particular clinical parameter associated with poor outcomes is part of the “causal” pathway or simply a marker of an overall poor prognosis is often difficult. In this study, the association between potassium levels and cardiac arrhythmias provides a potential “causal” link between potassium levels and increased short-term outcomes. In contrast, the admission potassium level may be more reflective of underlying comorbidities when evaluating the relationship with long-term outcomes. However, even with this limitation, it remains significantly associated with one-year mortality events after extensive modeling. Drugs, such as anti-arrhythmic drugs and diuretics, were not used in the multivariable model. In addition, cardiovascular deaths were not sub-classified as arrhythmic or non-arrhythmic in MERLIN-TIMI 36, thus preventing the further characterization of deaths. Further research is necessary to determine whether our results are applicable to patients with ST-elevation MI.

Our findings have demonstrated a relationship between potassium concentration and the risk of ventricular tachycardia and bradycardic events, which were inversely related to each other, suggesting that arrhythmogenic instability at either end of the potassium range and identifying 3.5–4.5 mEq/L as the most electrically “stable” range.

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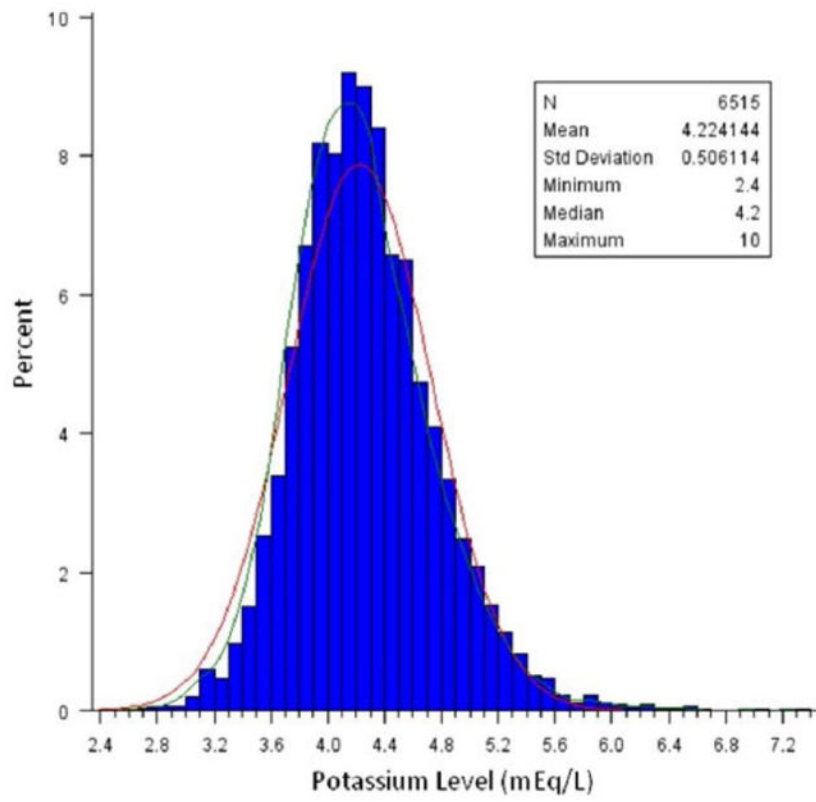
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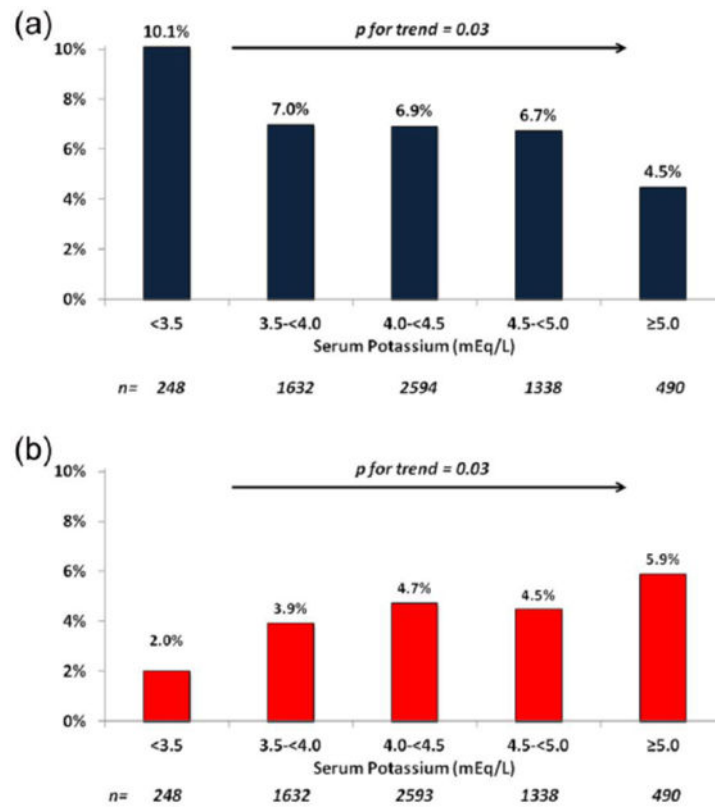
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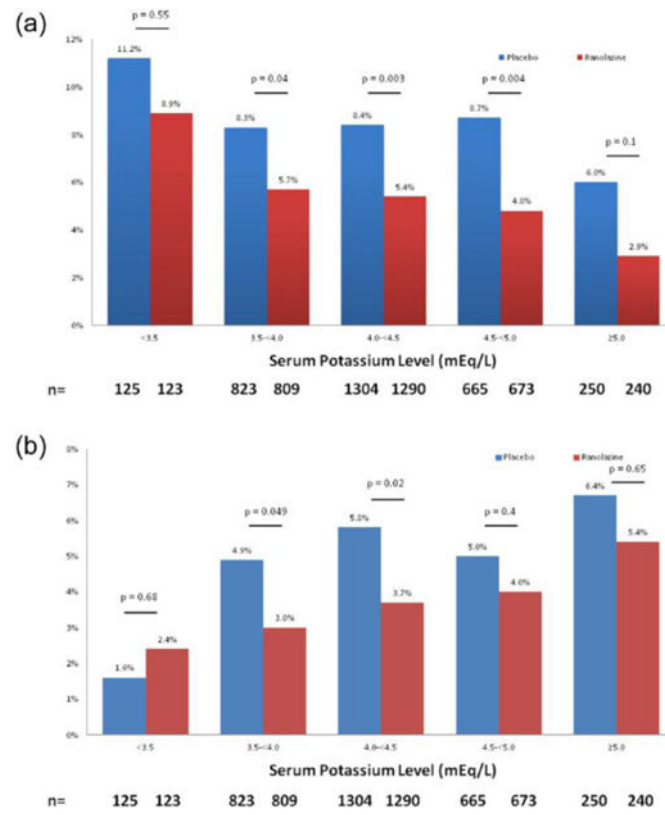




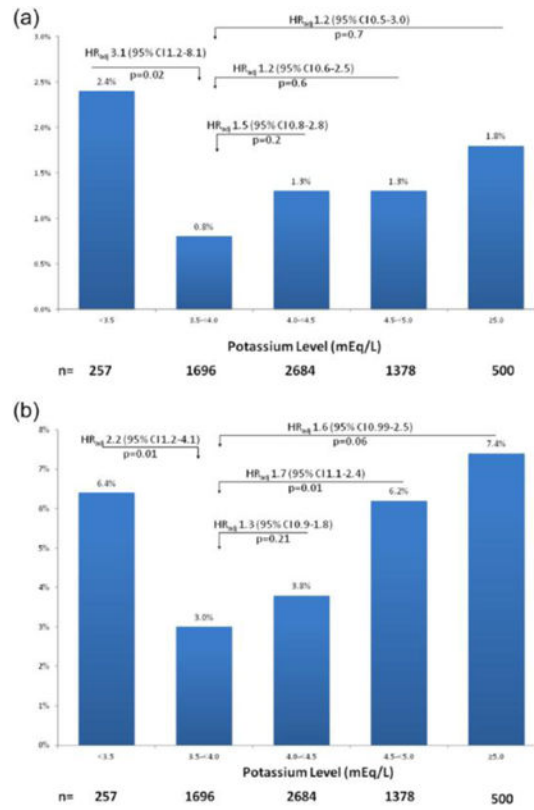
**Figure 1.**  
Distribution of potassium levels at admission.



**Figure 2.**  
 (a) Incidence of ventricular tachycardia ( $\geq 8$  beats) and (b) ventricular pauses  $\geq 3$  s based on potassium levels.



**Figure 3.** (a) Incidence of ventricular tachycardia  $\geq 8$  beats and (b) ventricular pauses  $\geq 3$  s in patients treated with ranolazine and a placebo.



**Figure 4.**  
 (a) Cardiovascular death at 14 days and (b) one-year based on potassium levels.

**Table 1**

Baseline characteristics of patients in MERLIN-TIMI 36 by potassium level.

Characteristic	Potassium levels (mEq/L)					p (trend)
	<3.5	3.5 to <4.0	4.0 to <4.5	4.5 to <5.0	≥5.0	
Female sex	114 (44.4)	626 (36.9)	855 (31.9)	489 (35.5)	196 (39.2)	0.3933
White ethnicity	230 (89.5)	1598 (94.2)	2562 (95.5)	1335 (96.9)	475 (95.0)	<0.0001
Diabetes mellitus	81 (31.5)	522 (30.8)	891 (33.2)	503 (36.5)	210 (42.0)	<0.0001
Hypertension	217 (84.4)	1234 (72.8)	1874 (69.8)	1044 (75.8)	407 (81.4)	<0.0001
Hyperlipidemia	167 (64.9)	1046 (61.7)	1704 (63.5)	830 (60.2)	281 (56.2)	<0.0001
Current smoker	54 (21.0)	423 (24.9)	722 (26.9)	335 (24.3)	129 (25.8)	<0.0001
Prior myocardial infarction	78 (30.4)	485 (28.6)	903 (33.6)	524 (38.0)	211 (42.2)	<0.0001
Prior coronary revascularization	68 (26.5)	447 (26.4)	741 (27.6)	367 (26.6)	109 (21.8)	<0.0001
Prior heart failure	33 (12.8)	238 (14.0)	385 (14.3)	289 (20.9)	143 (28.6)	<0.0001
Estimated creatinine clearance <60 mL/min	51 (19.8)	318 (18.8)	524 (19.5)	342 (24.8)	160 (32.0)	<0.0001
Unstable angina	120 (46.7)	758 (44.7)	1190 (44.3)	695 (50.4)	291 (58.2)	<0.0001
Non-ST-elevation myocardial infarction	133 (51.8)	900 (53.1)	1419 (52.9)	656 (47.6)	203 (40.6)	<0.0001
Other	4 (1.6)	38 (2.2)	75 (2.8)	27 (1.9)	6 (1.2)	<0.0001
TIMI risk score 0-2	63 (24.5)	511 (30.1)	765 (28.5)	314 (22.8)	95 (19.0)	<0.0001
TIMI risk score 3-4	143 (55.6)	876 (51.7)	1378 (51.3)	772 (56.0)	264 (52.8)	<0.0001
TIMI risk score 5-7	51 (19.8)	309 (18.2)	541 (20.2)	292 (21.2)	141 (28.2)	<0.0001
Coronary angiography during the index hospitalization	166 (64.6)	1106 (65.2)	1636 (60.9)	713 (51.7)	222 (44.4)	<0.0001
β blocker	232 (90.3)	1537 (90.6)	2391 (89.1)	1210 (87.8)	443 (88.6)	0.0234
Aspirin	249 (96.9)	1634 (96.3)	2574 (95.9)	1316 (95.5)	488 (97.6)	0.9236
Heparin	229 (89.1)	1570 (92.6)	2440 (90.9)	1218 (88.4)	440 (88.0)	0.0003
Glycoprotein IIb/IIIa receptor inhibitor	38 (14.8)	281 (16.6)	404 (15.1)	172 (12.5)	57 (11.4)	0.0005
Thienopyridine	166 (64.6)	1138 (67.1)	1804 (67.2)	814 (59.1)	260 (52.0)	<0.0001
ACE inhibitor or angiotensin II receptor blocker	205 (79.8)	1283 (75.7)	2083 (77.6)	1114 (80.8)	412 (82.4)	0.0004
Statin	228 (88.7)	1467 (86.5)	2290 (85.3)	1066 (77.4)	315 (63.0)	<0.0001
Ranolazine	126 (49.0)	848 (50.0)	1333 (49.7)	700 (50.8)	245 (49.0)	0.8750
Age (years)	63.00±11.2	62.97±11.1	63.05±11.1	64.38±10.9	65.27±10.6	0.061
Weight (kg)	84.18±18.5	82.06±15.7	82.80±15.9	81.94±15.8	80.92±17.1	0.069

Characteristic	Potassium levels (mEq/L)					p (trend)
	<3.5	3.5 to <4.0	4.0 to <4.5	4.5 to <5.0	≥5.0	
Body mass index	29.62±5.4	28.69±4.9	28.92±5.4	28.86±4.7	28.52±5.2	0.053

Data are presented as *n* (%) or mean±SD values.

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