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B-Type Natriuretic Peptide and the Effect of Ranolazine in Patients With Non–ST-Segment Elevation Acute Coronary Syndromes

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

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Objectives We designed a prospective evaluation of the interaction between B-type natriuretic peptide (BNP) and the effect of ranolazine in patients with acute coronary syndromes (ACS) as part of a randomized, blinded, placebo-controlled trial.

Background Ranolazine is believed to exert anti-ischemic effects by reducing myocardial sodium and calcium overload and consequently ventricular wall stress. BNP increases in response to increased wall stress and is a strong risk indicator in ACS.

Methods We measured plasma BNP in all available baseline samples (n = 4,543) among patients with non–ST-segment elevation ACS randomized to ranolazine or placebo in the MERLIN–TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST Elevation Acute Coronary–Thrombolysis In Myocardial Infarction 36) trial and followed them for a mean of 343 days. The primary end point was a composite of cardiovascular death, myocardial infarction, and recurrent ischemia. BNP elevation was defined as >80 pg/ml.

Results Patients with elevated BNP (n = 1,935) were at significantly higher risk of the primary trial end point (26.4% vs. 20.4%, $p < 0.0001$), cardiovascular death (8.0% vs. 2.1%, $p < 0.001$), and myocardial infarction (10.6% vs. 5.8%, $p < 0.001$) at 1 year. In patients with BNP >80 pg/ml, ranolazine reduced the primary end point (hazard ratio [HR]: 0.79; 95% confidence interval [CI]: 0.66 to 0.94, $p = 0.009$). The effect of ranolazine in patients with BNP >80 pg/ml was directionally similar for recurrent ischemia (HR: 0.78; 95% CI: 0.62 to 0.98; $p = 0.04$) and cardiovascular death or myocardial infarction (HR: 0.83; 95% CI: 0.66 to 1.05, $p = 0.12$). There was no detectable effect in those with low BNP (p interaction value = 0.05).

Conclusions Our findings indicate that ranolazine may have enhanced efficacy in high-risk patients with ACS identified by increased BNP. The interaction of biomarkers of hemodynamic stress and the effects of ranolazine warrants additional investigation. (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST Elevation Acute Coronary Syndromes; NCT00099788) (J Am Coll Cardiol 2010;55:1189–96) © 2010 by the American College of Cardiology Foundation

Elevated concentrations of B-type natriuretic peptide (BNP) and the N-terminal portion of BNP prohormone, early and late after presentation with an acute coronary syndrome (ACS), are strongly associated with an increased risk of recurrent cardiovascular (CV) events (1–5). Notably, increases in BNP and the N-terminal portion of BNP prohormone identify patients with ACS without systolic dysfunction or signs of heart failure who are at higher risk of death and heart failure and provide prognostic information that is complementary to clinical risk predictors and other biomarkers including cardiac troponin (1–3). Given this risk relationship, there

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Abbreviations and Acronyms

ACS = acute coronary syndrome
cECG = continuous electrocardiography
CI = confidence interval
CV = cardiovascular
HR = hazard ratio
MI = myocardial infarction
RR = relative risk

is intense interest in identifying treatments that might modify the risk associated with elevated concentrations of natriuretic peptides in patients with ACS (6,7).

Ranolazine is an antianginal that exerts anti-ischemic effects without a clinically significant effect on heart rate or blood pressure. At clinically relevant concentrations, ranolazine is an inhibitor of the late phase of the cardiac sodium current that is increased in myocardial ischemia and contributes to detrimental myocardial cellular sodium and calcium overload (8). In particular, disruption of sodium and calcium homeostasis can increase left ventricular diastolic tension and myocardial oxygen consumption (9,10). In animal models of ischemia/reperfusion, ranolazine ameliorates these adverse consequences, preserving tissue levels of adenosine triphosphate and improving myocardial contractile function (11). These findings suggested the hypothesis that ranolazine might mitigate the substantially higher risk of CV death and heart failure associated with elevated concentrations of BNP in ACS.

Therefore, we investigated the relationship between BNP and CV outcomes and the effect of ranolazine on that relationship as a prespecified exploratory analysis included in the design of the multinational, randomized, placebo-controlled MERLIN–TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST Elevation Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 36) trial (12).

Methods

Patient population. The design and primary results of the MERLIN–TIMI 36 trial were published previously (12,13). Eligible patients had at least 10 min of ischemic symptoms at rest and presented with one of the following: elevated biomarkers of myonecrosis, ST-segment depression ≥0.1 mV, a history of diabetes mellitus, or an intermediate to high (≥3) TIMI risk score. Exclusion criteria included persistent ST-segment elevation, end-stage renal disease requiring dialysis, cardiogenic shock, or a life expectancy <12 months. The protocol was approved by the relevant institutional review boards, and written consent was obtained from all patients.

Study treatment. Patients were randomized in a 1:1 ratio to receive ranolazine or matching placebo. After 12 to 96 h of an intravenous formulation, study medication (ranolazine extended release or placebo) was to be continued orally at a dose of 1,000 mg twice daily until the end of the study. Individuals with renal insufficiency (estimated creatinine clearance <30 ml/h) received 500 mg twice daily. Individuals received standard medical and interventional therapy as dictated by local practice guidelines. Randomization was stratified by the intention for early invasive management.

BNP testing. The protocol specified that blood samples be obtained at enrollment, on day 14, and at the final visit in ethylenediamine tetraacetic acid–anticoagulated plastic tubes and plasma isolated within 60 min of sample acquisition. Plasma samples were stored in plastic cryovials at −20°C or colder at the enrolling site until shipped to the TIMI Biomarker Core Laboratory (Boston, Massachusetts) where they were maintained at −80°C or colder. BNP was measured using the ADVIA Centaur (Siemens Healthcare Diagnostics, Inc., Deerfield, Illinois) (14) at the first thaw. The decision limit of 80 pg/ml was previously established as a cut point for risk stratification in ACS (1,2) and validated in multiple studies (7) including in our previous work with this particular assay (15). Levels of cardiac troponin I were measured using the TnI-Ultra assay (Siemens Healthcare Diagnostics, Inc.). The 99th percentile decision limit (0.04 ng/ml, <10% coefficient of variation) was used for all analyses consistent with current guidelines (16). All biomarker testing was performed in the TIMI Biomarker Core Laboratory by personnel blinded to clinical outcomes and treatment allocation.

End points. The primary efficacy end point of the trial was the composite of CV death, myocardial infarction (MI), and recurrent ischemia as defined previously (13). All components of the primary efficacy end point, as well as symptomatic documented arrhythmia, and new or worsening heart failure were adjudicated by a blinded clinical events committee. New or worsening heart failure was defined as rehospitalization or prolongation of the index hospitalization (≥24 h) in an acute care facility primarily for the treatment of heart failure along with an objective sign of heart failure (13). Exercise tolerance test results were interpreted by a core laboratory (St. Louis University Core Electrocardiographic Laboratory, St. Louis, Missouri) and continuous electrocardiographic recordings were evaluated in the TIMI Core Laboratory by reviewers blinded to treatment and outcome. Ischemia on continuous electrocardiography (cECG) was defined as ≥1 mm ST-segment depression lasting at least 1 min. Clinically significant arrhythmias were defined as ventricular tachycardia of at least 100 beats/min for ≥3 beats, supraventricular tachycardia of at least 120 beats/min for ≥4 beats, bradycardia of <40 beats/min, pauses of >2.5 s, or third-degree heart block (13). Ventricular tachycardias were further categorized according to number of beats (at least 4 beats, at least 8 beats) and duration <30 s (nonsustained) and >30 s (sustained) (17).

Statistical analysis. Plasma concentrations of BNP are reported using the median and interquartile range of values. The baseline characteristics of patients with and without elevated levels of BNP were compared using the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables. The associations between BNP

and clinical outcomes were evaluated using the log rank test, stratified by intention for early invasive management. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were estimated using a Cox proportional hazards regression model. Event rates are presented as Kaplan-Meier failure rates at 30 days and 12 months. The incidence of arrhythmias on cECG was evaluated using a Cochran-Mantel-Haenszel test. Commensurate with the primary statistical plan for the trial, all analyses of the effect of ranolazine were conducted stratifying by the intention to use an early invasive strategy before randomization. Testing for heterogeneity in the effect of ranolazine between patients with and without elevated levels of BNP was performed using Cox regression with terms for the main effects and for the interaction of BNP status with treatment allocation. This interaction was also assessed with adjustment for the effects of age, sex, diabetes, estimated creatinine clearance, body mass index, ST-segment depression on the presenting electrocardiogram, history of congestive heart failure, evidence of heart failure at presentation, and baseline cardiac troponin I result. In an exploratory analysis to assess the relative strength of the interaction with BNP, we also tested for heterogeneity of the effect of ranolazine with other plausible potential predictors of benefit: age, sex, diabetes, history of angina, index diagnosis, and ST-segment depression.

Analyses were performed using STATA version 9.2 (StataCorp., College Station, Texas). The p values (2-tailed) <0.05 were considered to indicate statistical significance.

Results

A total of 4,543 samples were available for determination of BNP concentration at enrollment occurring at a median (25th, 75th percentile) of 23 h (13 h, 33 h) from symptom onset. The median (25th, 75th percentile) concentration of BNP was 65 pg/ml (26, 147 pg/ml, respectively). The plasma concentration of BNP exceeded 80 pg/ml in 1,935 (42.6%) patients. The distribution of baseline BNP values was well balanced between treatment groups: 65 pg/ml (26, 148 pg/ml, respectively) for the placebo group and 65 pg/ml (27, 146 pg/ml, respectively) for the ranolazine group. Patients with an elevated concentration of BNP (>80 pg/ml) had multiple other indicators of high risk. They were older, more often female, and more likely to have a history of MI, heart failure, or diabetes (Table 1). At presentation, patients with elevated BNP more frequently had ST-segment depression, renal insufficiency, and a diagnosis of MI. Among those patients who underwent coronary angiography (n = 2,536), patients with elevated BNP were more likely to have multivessel (≥2) coronary artery disease (68% vs. 54%, $p < 0.001$), and disease involving the left anterior descending artery (74% vs. 64%, $p < 0.001$). Among patients with an assessment of left ventricular ejection fraction obtained as part of clinical care (n = 3,031), left ventricular ejection fraction was more commonly decreased (<40%) in those patients with elevated BNP (21.5% vs. 7.1%, $p < 0.001$). Baseline characteristics of patients were well balanced between the placebo and ranolazine groups among patients with BNP results from baseline (Online Table 1).

Table 1 Baseline Characteristics of Patients Stratified by BNP

Characteristics	BNP >80 pg/ml (n = 1,935)	BNP ≤80 pg/ml (n = 2,608)	p Value
Age, yrs	68 (60, 75)	60 (53, 68)	<0.001
Age ≥75 yrs	508/1,935 (26)	247/2,608 (9)	<0.001
Female sex	747/1,935 (39)	844/2,608 (32)	<0.001
White race	1,883/1,935 (97)	2,508/2,608 (96)	0.034
Weight, kg	80 (70, 89.5)	83 (74, 94.7)	<0.001
Risk factors for atherosclerosis			
Diabetes mellitus	661/1,935 (34)	8,17/2,608 (31)	0.044
Hypertension	1,465/1,927 (76)	1,896/2,591 (73)	0.030
Hyperlipidemia	1,129/1,757 (64)	1,662/2,369 (70)	<0.001
Current smoker	417/1,934 (22)	723/2,607 (28)	<0.001
Cardiac history			
Previous MI	749/1,910 (39)	859/2,588 (33)	<0.001
Previous coronary revascularization	516/1,933 (27)	695/2,606 (27)	0.98
Previous heart failure	449/1,935 (23)	486/2,608 (19)	<0.001
Estimated creatinine clearance <60 ml/min*	575/1,925 (30)	337/2,602 (13)	<0.001
Presenting syndrome			
Time from symptoms, h	24 (14, 34)	22 (12, 33)	<0.001
Non–ST-segment elevation MI	1,208/1,894 (64)	1,002/2,533 (40)	<0.001
ECG: ST-segment depression ≥0.1 mV	894/1,935 (46)	723/2,608 (28)	<0.001
TIMI risk score ≥4	1,128/1,935 (58)	1,018/2,608 (39)	<0.001

Data are expressed as median (25th, 75th percentile) or n/total (%). *Estimated using the Cockroft-Gault equation.
BNP = B-type natriuretic peptide; ECG = electrocardiogram; MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

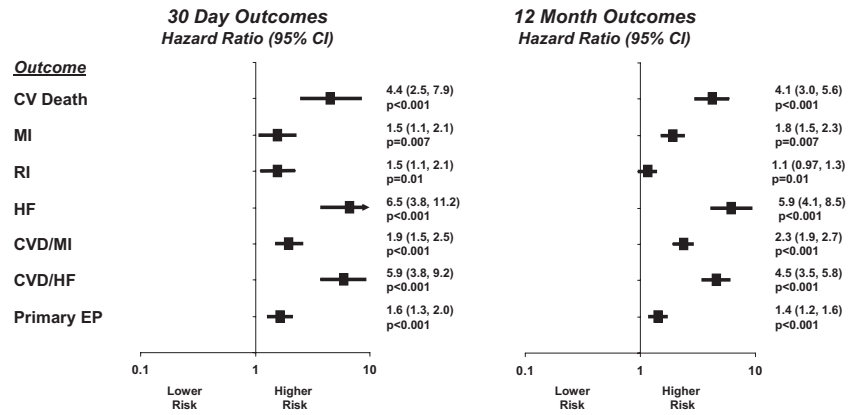

Figure 1 **Risk of 30-Day and 1-Year Adverse CV Outcomes Associated With Baseline BNP >80 pg/ml**

Primary end point (EP) is the composite of cardiovascular death (CVD), myocardial infarction (MI), or recurrent ischemia (RI). BNP = B-type natriuretic peptide; CI = confidence interval; CV = cardiovascular; HF = heart failure.

BNP and clinical outcomes. An elevated BNP concentration at enrollment identified a high-risk cohort of patients. Patients with baseline levels of BNP >80 pg/ml were at significantly higher risk of CV death, MI, or recurrent ischemia at 30 days ($p < 0.0001$) (Fig. 1) and at 1 year ($p < 0.0001$) (Fig. 2A). Patients with an elevated concentration of BNP at baseline were also more likely to have ischemia detected on continuous electrocardiographic monitoring during the first 7 days (26.8% vs. 17.3%, $p < 0.001$) and were at a higher risk of CV death, MI, or heart failure individually by 30 days and 1 year ($p < 0.001$ for each) (Fig. 1).

In addition, we found that an elevated BNP concentration was associated with a higher risk of the broad predefined composite arrhythmia end point (82% vs. 76%, $p < 0.001$) as well as a higher risk of ventricular tachycardia ≥8 beats (7.2% vs. 5.7%, $p = 0.037$), sustained ventricular tachycardia (0.75% vs. 0.24%, $p = 0.013$), supraventricular tachycardia (57% vs. 46%, $p < 0.001$), and atrial fibrillation (3.5% vs. 1.1%, $p < 0.001$). In addition to having a higher incidence of arrhythmias detected on cECG, patients with elevated BNP were also at higher risk of sudden cardiac death at 1 year (3.0% vs. 0.9%, $p < 0.001$). Patients with elevated BNP also had worse exercise performance (490 ± 250 s vs. 572 ± 266 s on treadmill testing, $p < 0.001$).

Effect of treatment with ranolazine. In the overall trial, the primary end point occurred in 21.8% of patients in the ranolazine group and 23.5% of patients in the placebo group by 1 year ($p = 0.11$), with a 13% reduction in recurrent ischemia favoring treatment with ranolazine (HR: 0.87; 95% CI: 0.76 to 0.99; $p = 0.03$) but no significant effect on the incidence CV death or MI ($p = 0.87$) (16). In this analysis based on BNP, ranolazine significantly reduced the primary end point (Fig. 2B) (HR: 0.79; 95% CI: 0.66 to 0.94) among the high-risk cohort of patients with BNP >80 pg/ml, in contrast to a lack of detectable effect of ranolazine in those with a negative BNP result (HR: 1.01; 95% CI: 0.85 to 1.20; p interaction = 0.05). Notably, this apparent effect of ranolazine in patients with elevated BNP was directionally similar for each element of the primary end

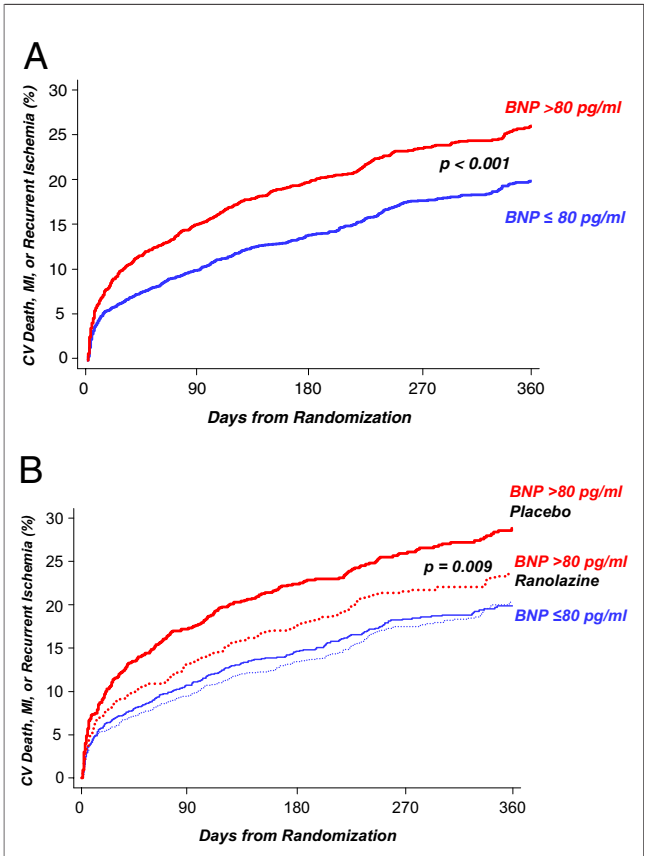

Figure 2 **Cumulative Incidence of Primary End Point**

Primary end point stratified by B-type natriuretic peptide (BNP) concentration at randomization **(A)** and both randomized treatment with ranolazine versus placebo and BNP **(B)**. CV = cardiovascular.

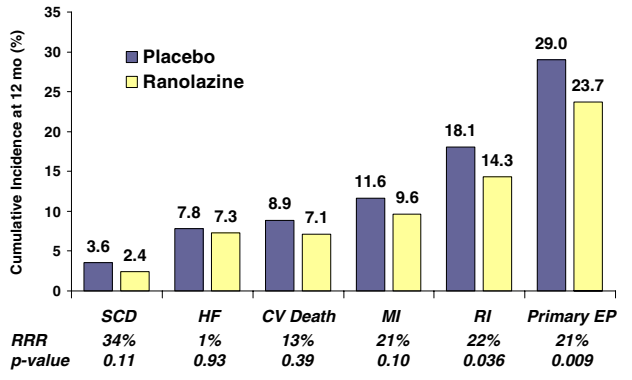

Figure 3 Kaplan-Meier Estimated 1-Year Incidence of CV Events

Sudden cardiac death (SCD), myocardial infarction (MI), recurrent ischemia (RI), and new or worsening heart failure (HF) with ranolazine compared with placebo among patients with baseline BNP results >80 pg/ml. RRR = relative risk reduction; other abbreviations as in Figures 1 and 2.

point (Fig. 3). Specifically, there was a similar but nonsignificant pattern of reduction in the end points of recurrent ischemia (HR: 0.78; 95% CI: 0.62 to 0.98; p interaction = 0.28) and CV death or MI (HR: 0.83, 95% CI: 0.66 to 1.05; p interaction = 0.067). There was, however, no detectable effect of ranolazine on the incidence of new or worsening heart failure in those with elevated BNP (HR: 0.99; 95% CI: 0.7 to 1.37; p interaction = 0.54).

In addition, the risk of arrhythmias on cECG in patients with elevated BNP was reduced with ranolazine (relative risk [RR]: 0.90; 95% CI: 0.86 to 0.94; $p < 0.001$, p interaction = 0.94). This effect included a consistent pattern of reductions across each type of arrhythmia, including ventricular tachycardia ≥8 beats (6.3% vs. 8.2%; RR: 0.78; 95% CI: 0.56 to 1.08; p = 0.13, p interaction = 0.33), supraventricular tachycardia (53.3% vs. 61.0%; RR: 0.88; 95% CI: 0.81 to 0.95; $p < 0.001$, p interaction = 0.095), and atrial fibrillation (3.1% vs. 3.8%; RR: 0.82; 95% CI: 0.51 to 1.34; p = 0.41, p interaction = 0.57) with ranolazine compared with placebo. Sudden cardiac death was numerically lower in the ranolazine group (HR: 0.66; 95% CI: 0.39 to 1.10; p = 0.11). There was no difference in exercise performance with ranolazine versus placebo (487 ± 248 s vs. 492 ± 252 s, p = 0.59) in those with elevated BNP.

Analysis of the change in BNP concentration from enrollment to 14 days and to the final visit (among survivors) revealed no significant difference between the ranolazine and placebo groups. The median change in BNP between day 0 and day 14 was 2 pg/ml in the ranolazine group and 0 pg/ml in the placebo group (p = 0.30). The respective values at the final visit were 7 and 9 pg/ml (p = 0.43). The results were similar when restricted to those patients with an initially elevated BNP (p = 0.51).

Multivariable assessment. To assess whether the observed benefit of ranolazine on the primary end point in patients with elevated BNP can be explained by other characteristics, we performed an adjusted analysis of the interaction between BNP and the randomized treatment. We found that after adjusting for age, sex, diabetes, history of angina, estimated creatinine clearance, body mass index, index diagnosis, ST-segment depression, and baseline cardiac troponin I result, the interaction term for BNP remained significant (p = 0.041). Testing of interaction terms for each of the other covariates revealed no other clinical characteristic that exhibited a stronger interaction with ranolazine than did BNP ($p > 0.15$ for all). Similarly, the extent of coronary artery disease among those who underwent coronary angiography for the index event (n = 2,536) was not significantly associated with the effect of ranolazine (p interaction = 0.73).

Discussion

In this nested prospective study of BNP in >4,500 patients, we found that, consistent with previous observations, patients who had an elevated BNP concentration at baseline were at substantially higher risk of adverse outcomes after non–ST-segment elevation ACS, including CV death, heart failure, recurrent ischemic events, tachyarrhythmias, and reduced exercise capacity. In this analysis of the interaction between baseline BNP concentration and outcomes with ranolazine, we found that ranolazine had a benefit among those patients with elevated BNP at presentation, with a significant reduction in the primary end point of CV death, MI, or recurrent ischemia. In contrast, in patients without elevated BNP, ranolazine had no effect on these outcomes. Ranolazine did not reduce the concentration of BNP over time nor the clinical end point of new or worsening heart failure. Nonetheless, BNP successfully identified patients at higher risk of recurrent myocardial ischemia that was ameliorated by ranolazine.

Natriuretic peptides in patients with myocardial ischemia. Myocardial ischemia is an important indirect and, possibly, direct stimulus for the synthesis and release of natriuretic peptides (6,18). In addition to increasing in the setting of spontaneous myocardial ischemia during ACS, the blood concentrations of BNP and the N-terminal portion of BNP prohormone also increase during provoked ischemia such as during exercise in patients with coronary disease (19–21) as well as after balloon inflation in uncomplicated coronary angioplasty (22,23). Moreover, the magnitude of the increase in BNP during stress testing is proportional to the size of the ischemic territory as assessed with nuclear single-photon emission computed tomography (19,20). Natriuretic peptide concentrations in patients with ischemic heart disease are also associated with the anatomic severity of coronary artery disease, including the number of diseased vessels and involvement of the proximal left anterior descending artery (2,24,25).

The adverse prognosis associated with increased concentrations of natriuretic peptides in patients with acute and

chronic ischemic heart disease has been well established (5,7,26). In addition, for the first time in patients with ACS, we found that patients who present with an elevated BNP concentration are at higher risk of clinically relevant arrhythmias and have diminished exercise performance. These latter findings are novel and highlight the broad range of morbidity associated with elevated natriuretic peptide levels among patients with ACS, even when clinical heart failure is not present. These findings across multiple studies have supported selective use of natriuretic peptides for risk stratification in patients presenting with ACS in whom additional prognostic information is desired (7). However, current guidelines for the use of biomarkers in patients with ischemic heart disease have not recommended routine measurement of natriuretic peptides because, to date, there has been no clear evidence that the results will influence treatment strategy (7). For these reasons, there has been strong interest in identifying therapies that specifically modify the risk associated with elevated concentrations of natriuretic peptides in this setting. Studies of the potential for revascularization to reduce the increased risk associated with elevated natriuretic peptides have produced mixed findings (2,27,28). Few studies have examined the impact of pharmacotherapy on outcomes in patients with ACS and elevated BNP (29).

Ranolazine and myocardial ischemia and function. Ranolazine inhibits the late phase of the sodium current in cardiac myocytes and has several actions that have raised the hypothesis that it might improve outcomes associated with myocardial dysfunction in ischemia and heart failure (8,13,30). Ranolazine enhances left ventricular systolic function and reduces left ventricular end-diastolic pressure in animal models of both heart failure and ischemia (11,31–34). We now report in this large prospective analysis nested in a randomized, placebo-controlled trial that the risk associated with elevated BNP was reduced with ranolazine. Interestingly, in this group of high-risk patients, in contrast with the overall trial results in which ranolazine had a neutral effect on CV death or MI, the pattern of event reduction was consistent with respect to CV death, MI, and recurrent ischemia individually, a finding that was statistically heterogeneous in those with BNP $<$80 pg/ml.

Although our hypothesis that ranolazine might offer a particular benefit in patients with increased ventricular wall stress as reflected in the concentration of BNP is supported by our findings, the mechanism of this benefit is not clear. We did not find evidence that the mechanism is related to a reduction in wall stress as a result of therapy in view of the absence of a detectable effect of ranolazine on BNP concentration over time and the lack of an effect on the end point of new or worsening heart failure in this study. An alternative explanation is that BNP is an integrative marker of the severity of coronary artery disease and the territory at risk of ischemia and other structural heart disease. This proposal is supported by our previous work (1,2,25) and that of others (3), which have linked natriuretic peptides to disease severity in patients with ischemic heart disease. As such, BNP may serve as a risk indicator that identifies ACS patients at high risk of adverse outcomes who have a greater probability of benefit from ranolazine with respect to ischemia, and perhaps arrhythmias, rather than necessarily through a significant direct reduction in hemodynamic stress.

Study limitations. Although the result of prespecified analyses, these intriguing findings must be regarded as inherently exploratory in the context of the overall trial's neutral primary result. Although the observation of a benefit of ranolazine with respect to the primary end point in those patients with elevated BNP is supported by testing for statistical heterogeneity ($p = 0.05$), the conclusiveness of the testing for heterogeneity should be interpreted in the context of multiple testing. It is possible that because the timing of BNP measurement was necessarily left flexible in the context of this multinational outcomes trial, a true effect of ranolazine on BNP was not detected because of confounding preanalytical variation. For these reasons, additional investigation is needed to corroborate the benefit of ranolazine in patients with elevated BNP that we observed in our study to determine potential optimal cut points of interaction and to define the possible mechanisms of benefit of ranolazine in these high-risk patients with ischemic heart disease. Specifically, the hypothesis that indicators of hemodynamic stress identify patients who may derive greater benefit from ranolazine requires prospective testing.

Conclusions

Patients with elevated natriuretic peptides at the time of presentation with an ACS are at substantially higher risk of poor outcomes. The results of this planned exploratory analysis suggest that ranolazine may reduce the risk associated with elevated BNP. The potential interaction between biomarkers of hemodynamic stress and the effects of ranolazine warrants additional study.

Author Disclosures

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Critical Diagnostics, CV Therapeutics, Sanofi-Aventis, Schering Plough, and Siemens; and is a paid member of a Clinical Events Committed for AstraZeneca. Dr. Scirica is a consultant for, educational presenter for, and has received research support from CVT/Gilead, and has received research support from Roche Diagnostics. Dr. Sabatine has received research support from CV Therapeutics and OrthoClinical Diagnostics. Dr. de Lemos has received grant support and consulting income from Biosite and Roche Diagnostics. Dr. Jarolim has received research support from Amgen, Beckman-Coulter, OrthoClinical Diagnostics, Roche Diagnostics, and Siemens Healthcare Diagnostics; and honoraria for educational presentations from Ortho-Clinical Diagnostics. Dr. Braunwald is the Chairman of the TIMI Study Group at the Brigham and Women's Hospital. Dr. Braunwald has received honorarium from Bayer AG, CV Therapeutics, Daiichi Sankyo, Eli Lilly, Merck & Co., Momenta, Schering-Plough, Sanofi-Aventis, Cytokinetics, Genzyme, GlaxoSmithKline, and Broadview Ventures.

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Key Words: angina ■ myocardial infarction ■ natriuretic peptides ■ ranolazine ■ unstable angina.

APPENDIX

For a table on the baseline characteristics in the ranolazine and placebo groups among patients with BNP measurement at baseline, please see the online version of this article.