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CORRESPONDENCE

Letters to the Editor

Ranolazine Is Effective for Acute or Chronic Ischemic Dysfunction With Heart Failure

We congratulate Morrow et al. (1) for their interesting study on the effects of ranolazine in patients with non–ST-segment elevation myocardial infarction. Ranolazine reduced the composite primary end point of cardiovascular death, myocardial infarction, and recurrent ischemia in patients with B-type natriuretic peptide >80 pg/ml. Interestingly, there was a decrease in composite arrhythmia end points consisting of ventricular tachycardia (>100 beats/min for >3 beats), supraventricular tachycardia (>120 beats/min for >4 beats), and bradycardia (<40 beats/min, pause >2.5 s or 3° atrioventricular block). Ranolazine usage showed a trend toward reduction across all arrhythmia types: ventricular tachycardia ($p = 0.13$), supraventricular tachycardia ($p < 0.001$), atrial fibrillation ($p = 0.4$), and sudden cardiac death ($p = 0.11$). These effects were observed over a mean duration of 343 days.

We recently reported successful use of ranolazine in a patient with chronic ischemic cardiomyopathy, symptomatic premature ventricular complexes (PVC [>36% of all beats]), and monomorphic ventricular tachycardia who had failed amiodarone and mexilitine therapy. Ranolazine decreased the total number of PVCs to 1% to 2% of all beats, eliminated the ventricular tachycardia, and led to complete resolution of symptoms (2).

Inhibition of the late sodium current (I_{Na}) is the proposed mechanism of both the anti-ischemic and anti-arrhythmic benefits of ranolazine. Activity in late I_{Na} activity is increased significantly in ischemia as well as congestive heart failure (3). Increased late I_{Na} activity produces higher intracellular sodium, which results in calcium overload through the sodium-calcium exchange. Ranolazine inhibits late I_{Na} 10-fold more selectively than peak I_{Na}. This mechanism, along with its β_1, β_2, and calcium-channel antagonism, produces its anti-ischemic and antiarrhythmic benefits (3).

The present study shows beneficial effects of ranolazine in the setting of acute ischemia with evidence of heart failure. Our patient had a chronic ischemic cardiomyopathy with severe myocardial dysfunction (ejection fraction 15%) for which ranolazine produced excellent symptomatic relief. Future studies using ranolazine are needed to evaluate patients with acute and chronic ischemia in the presence of elevated B-type natriuretic peptide/left ventricular dysfunction to further clarify its benefits. It may be this category of patients who have the highest risk–benefit ratio from ranolazine therapy.

Sudip Nanda, MD*
Matthew W. Martinez, MD
Tanujit Dey, PhD

*Lehigh Valley Hospital
Cardiovascular Medicine
1240 South Cedar Crest Boulevard
Allentown, Pennsylvania 18103
E-mail: sudipnanda2000@yahoo.com

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Reply

We appreciate the compliment and additional perspective from Dr. Nanda and colleagues regarding our paper (1). Patients with ischemic heart disease and left ventricular dysfunction, such as the patient described by Dr. Nanda and colleagues, are at substantial risk of major cardiovascular events, including sudden cardiac death. Moreover, they are at higher risk of proarrhythmia than patients with normal left ventricular function with multiple classes of antiarrhythmic medications, and they may poorly tolerate anti-ischemic medications with negative inotropic effects. We have also observed that patients with elevated levels of B-type natriuretic peptide are at particularly high risk of sudden cardiac death, even after accounting for left ventricular ejection fraction (2).

In pre-clinical studies, ranolazine has shown potentially favorable electrophysiological effects, such as a decrease in dispersion of repolarization, a reduction in action potential duration, and suppression of early after-depolarizations (3). In addition, in animal models of heart failure, ranolazine improves contractile function immediately after acute ischemia (4) and left ventricular ejection fraction in the setting of chronic ischemic heart failure (5).

We have shown previously that in patients with unstable ischemic heart disease, ranolazine significantly reduces the risk of ventricular and supraventricular tachycardia (3). Notably, we have also found that these effects on arrhythmias are present in patients at higher risk for tachyarrhythmia, such as those with elevated B-type natriuretic peptide (1) or a history of left ventricular dysfunction (3). These findings are consistent with the observations described by Dr. Nanda and colleagues. On the basis of these collective findings, we agree that the investigation of ranolazine in patients with ischemic heart disease and left ventricular dysfunction would be of substantial interest.

***David A. Morrow, MD, MPH**
Benjamin M. Scirica, MD, MPH

*TIMI Study Group/Cardiovascular Division
Brigham and Women's Hospital
75 Francis Street
Boston, Massachusetts 02115
E-mail: dmorrow@partners.org

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Are Angiotensin-Converting Enzyme Inhibitors and Beta-Blockers Ineffective in Children With Dilated Cardiomyopathy and Heart Failure?

In a retrospective, single-center study of children with dilated cardiomyopathy, Kantor et al. (1) compared outcomes in children treated with 3 different heart failure regimens (digoxin alone, digoxin and angiotensin-converting enzyme inhibitors [ACEI] but not beta-blockers [BB], and ACEI-BB combination) in a cohort of 189 patients. Because the study cohort represents their 30-year experience with dilated cardiomyopathy and different treatment regimens, the allocation to treatment groups was determined by the era of presentation and guided by the prevailing standards in adult heart failure therapy. On the basis of their observation that the transplantation-free survival time was similar among the 3 groups, the authors question whether evolving pharmacologic treatments for heart failure are as effective in improving survival in children with heart failure as they are in adults. Because ACEI and BB drugs are routinely used in pediatric heart failure, a closer examination of their analysis is important.

Unfortunately, there are at least 2 reasons to question the validity of their findings. Because the study center became a major referral center for heart transplantation halfway through the study, selection bias combined with selection of a composite end point likely biases the results toward the null. The more recent patients (those in the ACEI and ACEI-BB groups) are more likely to be those referred for heart transplantation and thus likely to have more severe heart failure. The similarity in ejection fraction among the 3 groups is not by itself compelling enough to eliminate this selection bias. Second, because the primary end point is a time-to-event composite outcome for death or transplantation, it changes halfway through the study when viewed from a clinical perspective. It is notable that almost all patients who reached the primary end point in the digoxin-only group died, whereas most patients in the ACEI and ACEI-BB groups reached the primary end point by receiving a heart transplant. Because the waiting list survival time without a transplant is highly variable and may be years in some patients listed for heart failure on oral heart failure therapy (those listed as Status 2 in the U.S. on the United Network of Organ Sharing wait list), transplantation could have artificially shortened the time-to-event outcome for several patients in the ACEI and ACEI-BB groups.

In randomized clinical trials, the comparison groups are similar in baseline characteristics, and the outcome difference can be attributed to the study drug alone. Moreover, the primary end point remains the same during the entire study duration. We recognize that it has been particularly difficult to conduct randomized clinical trials in children with heart failure because of the small number of children with heart failure. The largest randomized trial of a heart failure therapy in children was able to enroll only 161 children from 26 centers over a 4-year period of recruitment and was even then considered potentially underpowered by the authors to detect outcome differences (2). The difficulty in conducting large controlled trials in children with heart failure makes observational studies important. This study highlights the significant challenges faced by investigators with an observational study design.

***Tajinder P. Singh, MD, MSc**
Christopher Almond, MD

*Department of Cardiology
Children's Hospital Boston
300 Longwood Avenue
Boston, Massachusetts 02115
E-mail: tp.singh@cardio.chboston.org

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Reply

Drs. Singh and Almond engage in some useful conjecture, but their argument is not supported by published data, including our own (1). Much of their argument revolves around the possible interdependence of the choice for angiotensin-converting enzyme inhibitor (ACEI)/beta-blocker therapy and the selection bias for transplantation in "sicker" patients who may have been on these therapies. They speculate that the bias to perform transplantation on sicker patients undergoing treatment with ACEI/beta-blocker therapy artificially and negatively skewed the survival of these patients with the arrival of the transplant era.