EDITORIAL COMMENT

Three Decades of Clinical Trials With Beta-Blockers

The Contribution of the CAPRICORN Trial and the Effect of Carvedilol on Serious Arrhythmias*

Craig M. Pratt, MD, FACC
Houston, Texas

For the past three decades, the benefits of beta-blockers have been investigated in patients surviving acute myocardial infarction (AMI). Thanks to pioneering studies such as those in Scandinavia (timolol) (1), North America (propranolol—Beta-Blocker Heart Attack Trial [BHAT]) (2), and Europe (atenolol—First International Study of Infarct Survival [ISIS-I]) (3), a very compelling case was made by the mid-1980s for the use of beta-blockers in all appropriate post-AMI patients. The inclusion criteria for these trials were stable AMI patients. Patients with overt congestive heart failure (CHF) were excluded. Total mortality was reduced in all three trials, as well as death classified as “sudden.” Since the mid-1980s, the proliferation of new therapies for the treatment of myocardial infarction and coronary artery disease raises the question of relevance of these trials to contemporary therapy.

See page 525

At about the same time, the pathophysiology of clinical CHF due to left ventricular systolic dysfunction was clarified, and additional therapies focused on specific neuroendocrine targets. The angiotensin-converting enzyme (ACE) inhibitors, followed by angiotensin receptor blockers and spironolactone, were extensively studied and demonstrated to reduce mortality (4–6). Beta-blocker trials were subsequently extended from the postmyocardial infarction to the heart failure population. In the last 10 years, the U.S. carvedilol trials (7), Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) (8), and Effect of Carvedilol on Outcome After Myocardial Infarction in Patients with Left Ventricular Dysfunction (CAPRICORN) (9), all explored the benefits of the selective beta-blocker, carvedilol, in the polypharmacy environment of patients with heart failure. The former two studies were in heart failure populations with reduced left ventricular ejection fraction (LVEF); the CAPRICORN trial studied a post-AMI population with low LVEF (≤40%).

The CAPRICORN trial is the focus here, which consisted of patients with AMI within 5 to 21 days, and an LVEF ≤40% (9). Carvedilol was given in a dose escalation fashion ranging from 6.25 mg to 25 mg twice a day. The CAPRICORN trial was well executed and balanced for risk at baseline. Importantly, almost all patients (>98%) were taking an ACE inhibitor, and nearly one-half had received thrombolysis and/or primary angioplasty. Although the trial failed on its prespecified primary end point (all-cause mortality plus cardiovascular hospitalization: hazard ratio 0.92 [95% confidence interval 0.80 to 1.07]; p = 0.30), all-cause mortality was reduced 23% (p = 0.03) (9). New exploratory analyses on arrhythmia frequency are presented by McMurray et al. (10) in this issue of the Journal. An events committee blinded to treatment assignment verified arrhythmic events. In brief, the authors report a 59% reduction of atrial fibrillation/atrial flutter and a 76% reduction of ventricular tachycardia/ventricular fibrillation or flutter events in carvedilol-assigned compared with placebo-assigned patients. The arrhythmia reduction in carvedilol-assigned patients was consistent whether estimated as an intention-to-treat analysis or considering only patients without a history of preceding arrhythmia. The consistency of evidence from the CAPRICORN study, despite missing its primary end point, is that carvedilol is still beneficial after AMI therapy in the era of ACE inhibitors and interventional therapies (7). In fact, all-cause mortality was reduced by a magnitude (23%) nearly identical to the results using propranolol in the BHAT, published 22 years ago (2). “The more things change, the more they stay the same.”

What are the mechanisms by which carvedilol mitigates atrial and ventricular arrhythmias? Carvedilol blocks both beta1- and beta2-receptors. Unlike many other beta-blockers, carvedilol also possesses antioxidant, alpha-adrenergic blockade, and antiendothelin effects (7,8) and, in animal models, is reported to block the HERG potassium channel (11). Regardless of which of these mechanisms are operative, it is also important to consider indirect long-term hemodynamic effects of carvedilol, which may be pivotal in explaining the decrease in arrhythmias. These include a substantial increase in LVEF (by as much as 10%, absolute), decreased systolic and diastolic volumes, and, presumably, lower left ventricular filling pressure and left atrial mean pressure. The attenuation of remodeling by carvedilol on background therapy of ACE inhibition could be a major factor in decreasing atrial and ventricular arrhythmias.

A key focus is the interrelationships between arrhythmias, LVEF, and clinical CHF. The degree of systolic dysfunction is related to the extent of atrial and ventricular arrhythmias, a relationship long recognized from clinical trials (12) and from epidemiologic studies (13). The inci-

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From the Methodist DeBakey Heart Center and Baylor College of Medicine, Houston, Texas.
idence of atrial fibrillation in a heart failure population is related to the degree of CHF and LVEF. A stellar example is from the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) trials (myocardial infarction and CHF) (14,15) where the entrance requirement for LVEF was identical (<.35%), but the postmyocardial infarction population had an incidence of atrial fibrillation only one-quarter of the DIAMOND CHF trial population (7% vs. 27%) despite a small difference in mean LVEF (14,15). In the DIAMOND CHF trial, dofetilide-assigned patients had a reduction in atrial fibrillation that was associated with a reduction in heart failure hospitalization (15). Although this was a post-hoc analysis of the DIAMOND-CHF trial that did not meet its primary end point (all-cause mortality), it demonstrates the potential clinical importance of the interaction of atrial fibrillation and the degree of CHF.

Whether HERG potassium channel blockade plays a meaningful role in explaining the carvedilol-associated atrial fibrillation/flutter reduction is not known (11). A trial relevant to this possibility is the Azimilide Postinfarct Survival Evaluation (ALIVE), in which azimilide resulted in a reduction in recurrent or new atrial fibrillation (16). This was a prespecified analysis of a post-AMI population with LVEF ≤35% in whom nearly 90% of patients were on ACE and two-thirds of the patients were taking beta-blockers, randomly assigned to azimilide (an I_{Kr} and I_{Ks} blocker) versus placebo.

What about the reduction in ventricular tachycardia, ventricular fibrillation, and flutter in the CAPRICORN study? Again, history is revealing. A landmark epidemiologic study of patients after AMI by Bigger and colleagues (13) more than 25 years ago established that, as LVEF decreases, the extent and complexity of ventricular arrhythmias increases. In the Cardiac Arrhythmia Suppression Trial (CAST), ventricular arrhythmia suppression on antiarrhythmic therapy was more complete in patients with a preserved LVEF (12). It is a reasonable speculation that the reduction in ventricular arrhythmias in carvedilol-assigned patients is related to the beneficial effects of remodeling in the CAPRICORN trial. It is important to reemphasize that this was accomplished on a uniform background of ACE therapy (9).

We can expect the playing field of clinical trials in AMI and CHF to be conducted on increasingly complex background therapy. Despite the numerous additions to "required" therapies, the place of beta-blockers in the post-AMI population remains solid. The extension of beta-blockers to patients with left ventricular systolic dysfunction and symptomatic heart failure is also firmly established. Yet beta-blockers are still not as widely used as the data merits; why? One of the goals of the CAPRICORN investigations was to reestablish the role of beta-blockers in the vastly more complicated post-AMI therapeutic environment now facing clinicians. They accomplished their goal. So far the science of our clinical trials of beta-blockers has produced excellent results, whereas the public health goal of having all appropriate patients taking them has had more modest success.

Reprint requests and correspondence: Dr. Craig M. Pratt, The Methodist Hospital, Department of Medicine, 6565 Fannin, Mail Station F1001, Houston, Texas 77030. E-mail: cpratt@bcm.tmc.edu.

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