REFERENCES

1. Morrow DA, Scirica BM, Sabatine MS, et al. 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. J Am Coll Cardiol 2010;55:1189–96.
2. Scirica BM, Morrow DA, Karwatowska-Prokopczuk E, et al. Ventricular arrhythmias following non-ST segment elevation ACS and the relationship with sudden cardiac death in the MERLIN-TIMI 36 trial (abstr). J Am Coll Cardiol 2009;53:A121.
3. Scirica BM, Morrow DA, Hod H, et al. Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndrome: results from the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) randomized controlled trial. Circulation 2007;116:1647–52.
4. McCormack JG, Barr RL, Wolff AA, Lopaschuk GD. Ranolazine stimulates glucose oxidation in normoxic, ischemic, and reperfused ischemic rat hearts. Circulation 1996;93:135–42.
5. Sabbah HN, Chandler MP, Mishima T, et al. Ranolazine, a partial fatty acid oxidation (pFOX) inhibitor, improves left ventricular function in dogs with chronic heart failure. J Card Fail 2002;8:416–22.

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

doi:10.1016/j.jacc.2010.04.037

REFERENCES

1. Kantor PF, Abraham JR, Dipchand AI, Benson LN, Redington AN. The impact of changing medical therapy on transplantation-free survival in pediatric dilated cardiomyopathy. J Am Coll Cardiol 2010;55:1377–84.
2. Shaddy RE, Boucek MM, Hsu DT, et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. JAMA 2007;298:1171–9.

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.

However, the introduction of ACEI therapy in our series (1) occurred many years before (1983) the availability of heart transplantation, and in the case of beta-blocker therapy, most patients (1998 to 2004) began to receive this well after transplantation was established. Moreover, we showed that the patients most likely to die or receive a transplant were those who did not receive any oral agents. Regarding the propensity for transplantation, we have acknowledged this limitation, but have also shown that the advent of transplantation did not change the probability of the combined end point (death or transplantation) being reached when the pre-transplantation and current eras were compared. In addition, and contrary to their assertion, we did not show that patients receiving digoxin were more likely to die than to receive a transplant.

Drs. Singh and Almond's concern that transplant availability acts as a bias in treatment strategy is overwrought and also unsupported by any data. Almost every patient in our practice has undergone transplantation from a status of refractory heart failure, thus representing a de facto failure of medical therapy and justifying the concept of a composite end point. This concept is also broadly accepted in the pediatric cardiology literature (2,3).

We agree, however, that there has been a tendency to treat patients with these medications absent a compelling level of evidence, and we believe also that our experience is helpful in demonstrating equipoise regarding their effectiveness in this setting. Our data emphasize the need for adequately powered prospective randomized trials of therapy for children with this group of diseases.

***Paul F. Kantor, MB.BCh, DCH**

*Hospital for Sick Children
Cardiology, 1725 I
555 University Avenue
Toronto, Ontario M5G 1X8
Canada
E-mail: paul.kantor@sickkids.ca

doi:10.1016/j.jacc.2010.05.023

REFERENCES

1. Kantor PF, Abraham JR, Dipchand AI, Benson LN, Redington AN. The impact of changing medical therapy on transplantation-free survival in pediatric dilated cardiomyopathy. J Am Coll Cardiol 2010;55:1377–84.
2. Tsirka AE, Trinkaus K, Chen SC, et al. Improved outcomes of pediatric dilated cardiomyopathy with utilization of heart transplantation. J Am Coll Cardiol 2004;44:391–7.
3. Towbin JA, Lowe AM, Colan SD, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA 2006;296:1867–76.