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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.

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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.