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Editorial Comment

Paediatric heart failure trials…and tribulations

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The authors[1] present an interesting study of 33 patients who had undergone surgical repair of tetralogy of Fallot, and exhibited elevated levels of NT-pro brain natriuretic peptide, and reduced peak uptake of oxygen. The cohort was randomized either to placebo or treatment with bisoprolol. The authors should be congratulated for taking on the challenging task of performing a prospective and randomized trial in this group of patients. Clearly, this is an important group of patients who are becoming increasingly prevalent in the practice of paediatric cardiology and adult congenital heart disease. Bisoprolol is a highly selective antagonist of beta 1 adrenergic receptors, which has been shown to reduce mortality in adults with symptomatic congestive cardiac failure associated with left ventricular systolic dysfunction.[2] The authors hypothesized that bisoprolol would improve exercise capacity and reduce neurohormonal markers, such as the NT-pro brain natriuretic peptide, when compared to placebo.

Interestingly, there was no change in exercise capacity or ventricular ejection fraction. In addition, the clinical state did not change during treatment with bisoprolol. Surprisingly, those treated with bisoprolol showed significant increases in the levels of the brain natriuretic peptide in the plasma when compared to those randomized to receive the placebo. So, what conclusion are we able to draw from the study? Do the findings mean that bisoprolol is of no benefit in this clinical situation? Is it possible that bisoprolol is even deleterious, since the neurohormonal markers worsened during treatment with bisoprolol?

There are many challenges associated with studying patients in this type of setting. First of all, the number of patients available to be enrolled in a study of this kind is generally quite small. When compared to adults with coronary arterial disease, patients who have undergone surgical repair of tetralogy of Fallot represent only a fraction of this population. Thus, there is always a significant risk that a study of this kind may be underpowered to detect a difference in two treatment arms, if indeed such a difference is present. The population studied in this setting was different from those studied in most investigations of cardiac failure in that the patients were either asymptomatic, being in the first class of the categorization of the New York Heart Association, or mildly symptomatic, being in the second class. This clinical lack of symptomology is supported by the somewhat low levels of the brain natriuretic peptide found in the plasma of the patients. Thus, based on the minimal symptomology, it is harder to measure a response to therapy when initial symptomology is mild or none. The fact that the heart rates decreased during treatment with bisoprolol demonstrates that there was evidence of beta-blockade. Determining how this beta-blockade translates into improvements in symptoms, ventricular function, or survival is clearly more difficult.

Choosing a primary endpoint for these types of trials is one of the greatest challenges facing investigators who study children and young adults with congestive heart failure. Mortality is clearly not an option, since most trials of cardiac failure using mortality as a primary endpoint enroll 2,000 to 3,000 patients, the exception being the MOCHA

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trial.[2–5] Furthermore, it may not be realistic, even in a multicentric trial, adequately to study mortality in this population of patients, since mortality is really quite low. Thus, other surrogate endpoints, such as changes in the level of neurohormones such as the brain natriuretic peptides, or exercise, are often considered. Exercise, particularly, has been problematic as an endpoint in trials of cardiac failure. In the first two trials of beta-blockade in adults, submaximal exercise was the primary endpoint.[3,6] There was, however, no difference in the primary endpoint between carvedilol and placebo in these two studies, despite the fact that there was a significant benefit in terms of mortality in those who received carvedilol. Thus, a lack of improvement in exercise does not necessarily mean a lack of benefit from the drug. Unfortunately, there is yet to be a study that has demonstrated a benefit of any medication, such as an inhibitor of angiotensin converting enzyme, or a blocker of the angiotensin receptors, in patients with functionally single ventricles or systemic right ventricles.[7–9] Thus, the challenges that exist in studying this important group of patients are based on how one studies small groups. The Institute of Medicine recently published important concepts and recommendations in clinical trial design of small clinical trials.[10] This included recommendations that investigators be sure that the trial measures efficacy, reduces bias by randomization, includes control groups, uses blinding or an open-label trial, and ensures adequate sizes of the sample and statistical power. Although in theory these appear to be excellent recommendations, their practical application is quite difficult. For instance, there are no validated surrogate endpoints, or composite endpoints, in children with heart failure in clinical trials. In addition, how does one ensure adequately sized samples and statistical power when events are very low in a disease that is rare?

In summary, I congratulate the authors on their design and completion of this clinical trial. Unfortunately, as with many studies, it raises more questions than it answers. Although trite and overstated, these types of studies can only be answered if someone has the resources, expertise, and energy to recruit subjects in a multicentric, randomized, trial with validated and achievable endpoints.

References

1. Norozi K, Bahlmann J, Raab B, et al. A prospective, randomized, double-blind, placebo controlled trial of beta-blockade in patients who have undergone surgical correction of tetralogy of Fallot. Cardiol Young 2007; 17: current issue….
2. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999; 353: 9–13.
3. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. Circulation 1996; 94: 2807–2816.
4. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353: 2001–2007.
5. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002; 106: 2194–2199.
6. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group [see comments]. N Engl J Med 1996; 334: 1349–1355.
7. Kouatli AA, Garcia JA, Zellers TM, Weinstein EM, Mahony L. Enalapril does not enhance exercise capacity in patients after Fontan procedure. Circulation 1997; 96: 1507–1512.
8. Hechter SJ, Fredriksen PM, Liu P, et al. Angiotensin-converting enzyme inhibitors in adults after the Mustard procedure. Am J Cardiol 2001; 87: 660–663, A11.
9. Dore A, Houde C, Chan KL, et al. Angiotensin receptor blockade and exercise capacity in adults with systemic right ventricles: a multicenter, randomized, placebo-controlled clinical trial. Circulation 2005; 112: 2411–2416.
10. Small Clinical Trials: Issues and Challenges. Institute of Medicine, 2001. (Accessed at http://www.iom.edu/report.asp?id=5483).

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