posttransplant in the failed Fontan physiology patients might be due to various reasons.

First, an accurate determination of pulmonary vascular resistance is difficult in the failed Fontan patient population because of methodological inaccuracies that are implicit in the use of assumed oxygen consumption. Pretransplant pulmonary hypertension even in this modern era has consistently been a risk factor for poor outcomes.

Second, in our experience cardiac cirrhosis of the liver can occur especially in adults with failed Fontan physiology. Cardiac cirrhosis is variably encountered in adults with long-standing right heart failure and can be insidiously present and difficult to diagnose in the post-Fontan population owing to overlapping symptoms and signs attributable to the failed Fontan state, such as ascites, pleural effusions, and hypoproteinemia (4). Abdominal imaging studies such as computed tomography and ultrasound are useful in making the diagnosis by demonstrating a nodular liver. In selected cases, liver biopsy may be needed because the outcome of heart transplantation in patients with heart failure and dysfunction due to passive congestion of the liver is best determined by the extent of hepatic fibrosis demonstrated by histology (5).

Moreover, patients with significant cirrhosis have abnormal coagulation profiles, are prone to infections, and can suffer from hepatic decompensation postoperatively, thus adversely impacting survival following heart transplantation. It is therefore important to recognize the concept of cardiac cirrhosis and seek it in the failed Fontan patient who is being considered for heart transplantation. This may enable not only risk stratification but also, in severe cases, consideration of aggressive approaches such as combined heart and liver transplantation to help improve posttransplant survival in these high-risk patients.

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REPLY

We appreciate the thoughtful comments from Drs. Pereira and Shirali on our recent article (1) and would like to take this opportunity to respond.

The power to detect significant differences in posttransplant survival between the Fontan patients and other etiologies was limited by the small number of Fontan patients (n = 24), and further subanalyses by type of surgery and era of transplant were not feasible. Congenital heart disease has consistently been identified as a risk factor for one-year mortality according to reports of the International Society for Heart and Lung Transplantation (2). The majority of patients with congenital heart disease undergoing transplantation have complex disease and single-ventricle physiology. Similar to our data, conditional survival after one year was not significantly different for the congenital heart disease patients compared to others.

Pulmonary resistance is often impossible to determine in this group of single-ventricle patients with multiple sources of pulmonary blood flow; however, mortality from right heart failure was not a cause of death in our series, except in the single patient who had undergone a Fontan takedown procedure for pulmonary hypertension. It is difficult to imagine that a patient who is surviving, even poorly, with Fontan physiology would have significant enough pulmonary hypertension leading to right heart failure following implantation of a two-ventricle heart.

Long-standing hepatic venous congestion was common among patients in our series. The mean pretransplant prothrombin time was 14.6 ± 2 s, with a range of 11 to 18 s and an international normalized ratio of 1.7 ± 0.7, with a range of 1 to 2.9. There was no difference in the preoperative coagulation profile among the three patients who died from hemorrhage and the other Fontan patients. Subtle abnormalities of coagulation may have been present in these patients; however, other causes of postoperative hemorrhage such as prolonged cardiopulmonary bypass time and perfusion injury to the liver may also have played a role.

Additional data from multicenter registries, such as the Pediatric Heart Transplant Study Group, will soon be available that allows further risk stratification for posttransplant outcome in these complex patients, and continued efforts to define the criteria for transplantation are essential (3). We appreciate the opportunity to respond to the letter by Drs. Pereira and Shirali.

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Economic Effects of Extended Clopidogrel Therapy—A Word of Caution

In the February 1 issue of the *Journal*, Cowper et al. (1) compared the outcomes and costs of extending clopidogrel therapy (in addition to aspirin) from one month to one year after percutaneous coronary intervention (PCI), with withdrawal of clopidogrel after one month. Unpublished per-protocol data from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial (2) were used to estimate the effects of long-term clopidogrel use on event rates in a sample of patients at the Duke Medical Center undergoing PCI and receiving clopidogrel for only one month after the procedure. The investigators concluded that clopidogrel therapy for one year after PCI is economically attractive in respect to cost per year of life saved, particularly in high-risk patients.

However, the conclusions of Cowper et al. (1) rest solely on the assumption that clopidogrel between one month and one year after PCI significantly reduces the incidence of myocardial infarction (MI). The relative risk (RR) of MI was estimated to be 0.56 with clopidogrel long-term, but the 95% confidence interval (CI) was 0.3 to 1.0, suggesting a possibility of no effect at all. Consequently, the costs per year of life saved may actually be unlimited, as shown in Figure 2 in the study by Cowper et al. (1). Moreover, by using per-protocol rather than intent-to-treat data, an even distribution of confounders produced by randomization was altered, which may have incorrectly favored extended clopidogrel therapy. In fact, the one-year intention-to-treat analysis of the CREDO trial did not show a significant reduction of MI between day 0 and one year or between one month and one year (RR reduction between day 0 to one year, 21.7%; 95% CI −7.1% to 42.7%) (2,3). Similarly, the observational PCI substudy of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial (4) did not show an advantage of long-term clopidogrel use over placebo in terms of death or MI beyond 30 days after PCI (RR reduction 23%; 95% CI, −17% to 50%) (5).

An increase of major bleeding occurs when clopidogrel is added to aspirin long-term (2,6,7), and bleeding (like MIs) may influence prognosis adversely (8). Only the costs of bleeding, but not a potential negative effect on life expectancy, were incorporated into the model used by Cowper et al. (1). In addition, the low compliance with therapy in the CREDO trial (~60%) may have obscured the true risk of severe bleedings with dual antiplatelet therapy.

Finally, the conclusions of Cowper et al. (1) should be viewed with caution—they seem overenthusiastic and may be incorrect. Health economics cannot help to guide decisions on therapy when there is no firm evidence of clinical efficacy. Combining clopidogrel and aspirin long-term may actually do more harm than good.

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REPLY

Dr. Eriksson is correct in noting that our results hinge on the ability of clopidogrel to reduce the incidence of myocardial infarction (MI) between one month and one year after percutaneous coronary intervention (PCI), a point we emphasized in our report (1). Although Dr. Eriksson is also technically correct in pointing out that, as the confidence interval for relative risk (RR) for MI ranged from 0.3 to 1.0, there is a possibility that Clopidogrel has no effect on MI, we do not consider this to be a likely scenario. The point estimate (0.56) is the best estimate of RR. Because the Clopidogrel for the Reduction of Events During Observation (CREDO) trial was not powered to detect differences in individual components of the combined end point, borderline significance ($p = 0.05$) for MI, one of the components, is not surprising.

Dr. Eriksson also expressed concern that the per-protocol population may not have been balanced between groups with respect to confounders, causing the analysis to favor clopidogrel therapy. However, we found no differences between the treatment groups in baseline clinical characteristics of per-protocol patients. Furthermore, although the reduction in MI between one month and one year in the intention-to-treat population was not signif-