

REFERENCES

1. Jayakumar KA, Addonizio LJ, Kichuk-Christant MR, et al. Cardiac transplantation after the Fontan or Glenn procedure. *J Am Coll Cardiol* 2004;44:2065-72.
2. Boucek MM, Edwards LB, Keck BK, et al. Registry for the International Society for Heart and Lung Transplantation: Seventh Official Pediatric Report—2004. *J Heart Lung Transplant* 2004;23:933-47.
3. Bernstein D, Naftel D, Chin C, et al. Pediatric Heart Transplant Study Group. Outcome of listing for cardiac transplantation for failed Fontan: a follow-up multi-institutional study. *J Heart Lung Transplant* 2004;23 Suppl:S162.

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 Unpublished per-protocol data from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial (2) were used to estimate the effects of long-term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 clopi-

dogrel and aspirin long-term may actually do more harm than good.

***Peter Eriksson, MD, PhD**

*Interventional Cardiology Laboratory
Heart Center
University Hospital
SE-901 85 Umea
Sweden
E-mail: peter.eriksson@medicin.umu.se

doi:10.1016/j.jacc.2005.07.004

REFERENCES

1. Cowper PA, Udayakumar K, Sketch MH Jr., Peterson ED. Economic effects of prolonged clopidogrel therapy following percutaneous coronary intervention. *J Am Coll Cardiol* 2005;45:369-76.
2. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial [erratum in *JAMA* 2003;289:987]. *JAMA* 2002;288:2411-20.
3. Eriksson P. Long-term clopidogrel therapy after percutaneous coronary intervention in PCI-CURE and CREDO: the "Emperor's New Clothes" revisited. *Eur Heart J* 2004;25:720-2.
4. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527-33.
5. Stables RH. Clopidogrel in invasive management of non-ST-elevation ACS. *Lancet* 2001;358:520-1.
6. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
7. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004;364:331-7.
8. Kinnaird TD, Stabile E, Mintz GS, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. *Am J Cardiol* 2003;92:930-5.

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-